

FIG. 1



The infectious mucous patches of early syphilis are hardly marked grayish erosions usually not painful and often unrecognized. Upon the early diagnosis of these lesions depend the future welfare of the patient. Page 93

INTERNATIONAL CLINICS

A Quarterly

OF

ILLUSTRATED CLINICAL LECTURES AND
ESPECIALLY PREPARED ORIGINAL ARTICLES

ON

TREATMENT, MEDICINE, SURGERY, NEUROLOGY, PÆDIATRICS, OBSTETRICALS, GYNAECOLOGY, ORTHOPÆDICS, PATHOLOGY, DERMATOLOGY, OPHTHALMOLOGY, OTOTOLOGY, RHINOLOGY, LARYNGOLOGY, HYGIENE, AND OTHER TOPICS OF INTEREST

BY LEADING MEMBERS OF THE MEDICAL PROFESSION
THROUGHOUT THE WORLD

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VOLUME III FORTY-SEVENTH SERIES, 1937

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The infectious mucous patches of early syphilis are sharply marked grayish erosions, usually not painful and often unrecognized *Frontispiece*, page 1

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Medical Clinics at the Johns Hopkins Hospital, Baltimore, Maryland*

I Amoebic Hepatitis

By THOMAS B FUTCHER, M D

Visiting Physician

and

A M HARVEY, M D

Assistant Resident Physician

CASE presented by Dr A M Harvey

This patient is a twenty-six year old colored chauffeur who was admitted to the hospital on October 30, 1936, complaining of severe pain in the right upper quadrant of the abdomen of four days' duration. He has had no serious illnesses in the past. Five months ago the patient had a penile lesion but frequent Wassermann tests taken since that time have all been negative. For the past two years he has had occasional attacks of indigestion. These appear about once each month, consist of epigastric pain which comes on about one o'clock in the morning, and is quickly relieved by drinking warm water. He passed a black-looking stool on two occasions during the month prior to his admission. There was no history of his ever having had diarrhoea or dysenteric symptoms. The patient has never been out of the city of Baltimore.

Four days before coming to the hospital, while standing quietly, he developed a sudden sharp pain in the epigastric region which radiated to the right side of his chest. The pain was continuous in character and was not associated with nausea, vomiting or diarrhoea. The following day the pain appeared only when he inspired, and he noticed a dull ache in the region of his right shoulder. Fever, headache, and general malaise were present, but he had no chill or cough. The pain persisted, and he finally came to the hospital for treatment on the fifth day of his illness.

* Presented before the Southern Medical Association, November, 1936

Physical examination revealed the following points of interest temperature 102, pulse rate 85, respiratory rate 20. The patient looked ill, was complaining of sharp pain in the right upper quadrant of the abdomen brought on by inspiration, but he was in no acute distress. The skin was warm and moist, and the mucous membranes were of good color. There was no jaundice and no cyanosis. The tonsils were slightly enlarged. The heart and lungs were entirely normal. The main interest of the examination centered in the abdomen. The upper portion moved very little with respiration. There was marked tenderness to light palpation, muscle spasm, and rebound tenderness below the costal margin on the right. No masses could be felt but the liver edge was percussed 4 cm below the costal margin in the mid-clavicular line. The remainder of the abdomen was soft. No tenderness was present on rectal examination, and no masses were felt. There was no peripheral edema, or clubbing of the fingers. The reflexes were equal and active.

The laboratory studies were as follows:

Urine Clear, amber, specific gravity 1.022, acid, negative for sugar, albumin, bile, urobilin, acetone, microscopic examination—occasional white cell.

Blood Red blood cells 4,260,000, white blood cells 17,500, hemoglobin 12 Gm (83 per cent). Differential count juvenile polymorphonuclears 2 per cent segmented polymorphonuclears 78 per cent, eosinophils 2 per cent, lymphocytes 11 per cent, mononuclears 7 per cent. The red blood cells were normal in size, shape, and hemoglobin content. No malarial parasites were seen. No sickle cells were seen.

The *Wassermann reaction* was negative.

The *Van den Bergh reaction*, the nonprotein nitrogen and the carbon dioxide combining power of the blood were normal.

A *bromsulphalein excretion test of liver function* showed 40 per cent retention of the dye thirty minutes after injection.

A culture of the blood, urine, and stool showed no pathogenic organisms. The serological tests for typhoid, paratyphoid A and B and for undulant fever were negative.

Roentgen Ray Reports Chest The lungs are clear. The diaphragms are in normal position.

Abdomen The film of the abdomen is negative

The patient continued to have a temperature ranging between 102° and 103° F, the leukocytosis persisted, but the tenderness and pain abated a little, and the pulse rate remained normal. It was felt that these facts excluded the possibility of the illness being due to a perforating ulcer or empyema of the gallbladder, and it was thought that diffuse hepatitis with perihepatitis was the most likely diagnosis. The stools were examined daily. They were always normal in character and contained no amoebae until the sixteenth day of his illness. At that time a few flecks of mucus were passed which were found to contain numerous *Entamoeba histolytica* cysts. Numerous active forms of *Giardia Lamblia* were also present. A second stool passed the same day also contained large numbers of cysts, but no actively motile forms were present.

The patient was immediately started on a course of emetine hydrochloride. Twenty-one mg of the drug were given by subcutaneous injection three times a day for a period of ten days. After a few doses had been administered symptomatic improvement was apparent. The patient volunteered the fact that he felt much better, the pain gradually disappeared, his appetite improved, and three days later his leukocyte count was normal for the first time. A protoscopic examination was done. No actual ulcerations were present in the mucosa of the rectum and lower sigmoid but the surface appeared pale, a little swollen, and bled freely after slight traumatization.

At the termination of the emetine medication a course of yatren was given both by mouth and by retention enema. Upon discharge he was told to take carbarsone 0.25 Gm twice daily for a period of ten days.

After the first day of active treatment no amoebic cysts could be found in the stools, and there has been no return of symptoms. The final liver function test showed only 15 per cent retention of the dye at the end of one half hour.

This case is presented as one of amoebic infection in which the initial symptom was the onset of sudden abdominal pain associated with acute hepatitis, and in which no gastro-intestinal manifestations appeared until the sixteenth day of the illness.

REMARKS BY DR. THOMAS B. FUTCHER

In commenting on this case, may I first call your attention to the fact that the most important early work in amoebiasis in this country was carried out by members of the staff of this hospital. The institution was opened for the admission of patients in May, 1889. In America, amoebae were first found by Osler¹ who discovered them in 1890 in the pus of a liver abscess originating in Panama and operated on by Louis McLane Tiffany, of Baltimore. In 1891 Councillman and Lafleur² published their classical monograph on amoebic dysentery, based on the clinical and pathological study of cases in this hospital, and in which they gave the name *amoeba dysenteriae* to the intestinal parasite.

As the history of the present case was presented to you, I am sure that various possibilities entered your minds, as they did ours, concerning the cause of his symptoms. We had to consider cholelithiasis, cholecystitis, gastric or duodenal ulcer with perforation, syphilitic fever with gumma of the liver, and various bacterial infections. By clinical observation and laboratory studies these were one by one excluded.

The final discovery of cysts of *Entamoebae histolytica* in the stools on the sixteenth day of the patient's illness, even after numerous previous negative findings, emphasizes the importance of repeated stool examinations for amoebae in a patient with fever, upper right quadrant pain and pain radiating to the right shoulder, owing to the possibility of secondary amoebic infection of the liver. This must be emphasized even though there has been no history of diarrhoea or dysentery. There was no such history in this patient.

I observed this case personally first at Ward Rounds on November 14th. As cysts of *Entamoebae histolytica* had just been found in the stools the case was particularly studied from the standpoint of the liver. The liver dullness extended from the sixth rib to a point 3 to 4 cm below the costal margin in the midclavicular line, showing slight enlargement downwards. There was little or no tenderness in the upper right quadrant at this time. The question had to be considered whether the patient might have an amoebic abscess of the liver or whether he might have an amoebic hepatitis. As there was no evidence of any increase in the height of the liver dullness posteriorly and as there was no elevation of the height of the diaphragm on the

right side in the roentgenogram, we were inclined to the view that the patient had an amoebic hepatitis rather than one or more amoebic liver abscesses. This conclusion had been arrived at by Dr. Harvey and has been borne out by the satisfactory response to the specific amoebic treatment instituted. The upper right quadrant pain, with reflex pain transmitted to the right shoulder, seems undoubtedly to have been due to amoebic hepatitis.

It is interesting to note that this patient, in addition to having intestinal amoebiasis, had also another protozoan intestinal infection, viz., girardiasis. This is due to the parasite *Lamblia intestinalis* or *Girardia lamblia*. It is a ciliated organism 12 by 18μ in length and 6μ in breadth. It infests the small intestine, particularly the duodenum, and, in rare instances, may invade the gallbladder producing cholecystitis. Historically, it is important to note that Lambl was the first to describe this organism, as well as the amoeba, in 1859.

Although Losch, in 1873, was the first accurately to describe amoebae in the stools, it is well to remember that many intestinal amoebae are non-pathogenic. It is also important to remember that our present nomenclature of intestinal amoebae comes from Schaudinn, who first discovered the specific cause of syphilis, the *treponema pallidum*, in 1905. In 1902, Schaudinn gave the name *entamoeba coli* to the non-pathogenic form, and *entamoeba histolytica* to the pathogenic form. In the examination of the stools of amoebic dysentery patients we may find either actively motile amoebae, called trophozoites, or inactive cysts of amoebae, as in this case. The spread of amoebic infections is probably never due to the former, as the actively motile forms are soon destroyed outside the body, and when ingested are promptly destroyed by the gastric juice. It is the cystic forms that are probably entirely responsible for the transmission of the infection, as they may remain viable under favorable conditions outside the human body for about ten days. Desiccation kills them immediately. The cysts will develop and exist *in vitro* in Drbohlav's medium under proper conditions. When the cysts are swallowed by another human host they pass into the intestines, where they hatch and develop amoebulae, which in turn invade the intestinal wall and recommence the cycle.

The profession does not sufficiently realize the incidence of amoebiasis in this country. It is estimated that approximately 10 per

cent of the population have the disease. In certain parts of the country, particularly the South, it is probably even more prevalent. It is not exclusively a tropical disease, as it frequently originates in the temperate zones. The vast majority of the cases in this hospital have developed the infection within the borders of the State of Maryland. This comparative prevalence of the disease, therefore, emphasizes the importance in puzzling cases even without diarrhoea, of frequent and painstaking microscopic examination of the stools for the trophozoites and the pre cystic and cystic forms. The cysts were found in this patient only after repeated examination of the stools.

Great advances have been made in the treatment of amoebiasis in the last twenty-five years. Previous to that date the treatment was by high bowel irrigations with solutions of quinine sulphate. In severe cases of intractable dysentery sometimes an appendicostomy was performed and quinine irrigations were introduced through the appendicostomy opening daily, in order more effectively to reach the ulcerated colon. The quinine treatment was only moderately effective and was abandoned in a few years.

In 1911 a great advance in therapy was made. Vedder³ that year in Manila discovered that the amoebae were readily destroyed by emetine. The following year, 1912, Leonard Rogers⁴ demonstrated the great efficiency of emetine hydrochloride in the treatment of intestinal and hepatic amoebiasis in India. He found it not only most efficient in relieving the intestinal features but also in cutting short the symptoms of amoebic hepatitis. It is well to remember that even before 1911 ipecac, by oral administration, had already been used with very considerable success, but this procedure was objectionable owing to the nausea and vomiting likely to be produced.

Since Vedder's important contribution, treatment with emetine hydrochloride has come into general use as one of the measures for the treatment of amoebiasis and has been most satisfactory. The drug is often almost as specific as is quinine in malaria. Whereas various directions for its use are given, a very satisfactory method is to give 21 mg (1/3 gr) hypodermatically three times a day for ten days. This was the procedure carried out in this patient, with great benefit particularly to the liver manifestations. Owing to the tendency of amoebic dysentery to relapse it is wise to give one or two other courses after intervals of seven to ten days. In an active dysen-

tery with numerous amoebae in the stools, the diarrhoea or bloody stools promptly cease and the amoebae rapidly disappear. Manson-Bahr states that emetine is a much more effective amoebicide in metastatic amoebic lesions than it is in amoebic dysentery, and, therefore, is most efficacious in the hepatic complications, especially if used in the early stages.

Emetine-bismuth-iodide is sometimes used as a substitute for emetine hydrochloride. It may be given by mouth in 1 gr capsules three times daily for a period of eight to ten days.

Other remedies have also come into use in recent years. In 1921 Muhlens and Menk introduced yatren (chiniofon). Chemically it is iodo-oxy-quinolin sulphonic acid with an iodine content of about 28 per cent. It is given by mouth in keratin capsules or keratin coated pills in doses of 0.25 Gm (4 gr) three times daily for seven to ten days. With the oral administration of the drug it should also be given rectally at intervals of ten days. Reed advises washing out the lower bowel thoroughly with a 2 per cent solution of bicarbonate of soda and then introducing 180 cc of warm water containing 5 Gm. of yatren and have the patient retain the drug over night.

It is interesting that our patient for the first three days after admission to the hospital had a temperature that reached to 102° or 103° daily. Owing to his fever the possibility was entertained that he might have syphilitic fever with a gumma of the liver. He was accordingly started on iodide of potassium on the third day after admission when he had 2 Gm., with 3 Gm. daily afterwards. This was before the Wassermann was known to be negative and before the amoebic cysts were found. The temperature dropped very materially in the first twenty-four hours and remained much lower. As yatren contains iodine, we later speculated whether the drop in temperature following the administration of iodide of potassium may have been due to the influence of iodine acting as an amoebicide.

In recent years certain arsenical preparations have also come into use in the treatment of amoebiasis. One of these is stovarsol. It is given in tablets containing 0.25 Gm (4 gr) twice daily for ten days. The other is carbarsone and is given in the same size doses in capsules for the same length of time. A course of one or the other of these two drugs may be used as a substitute for yatren after the preliminary course of emetine has been carried out. It is claimed for them that

cent of the population have the disease. In certain parts of the country, particularly the South, it is probably even more prevalent. It is not exclusively a tropical disease, as it frequently originates in the temperate zones. The vast majority of the cases in this hospital have developed the infection within the borders of the State of Maryland. This comparative prevalence of the disease, therefore, emphasizes the importance in puzzling cases even without diarrhoea, of frequent and painstaking microscopic examination of the stools for the trophozoites and the precystic and cystic forms. The cysts were found in this patient only after repeated examination of the stools.

Great advances have been made in the treatment of amoebiasis in the last twenty-five years. Previous to that date the treatment was by high bowel irrigations with solutions of quinine sulphate. In severe cases of intractable dysentery sometimes an appendicostomy was performed and quinine irrigations were introduced through the appendicostomy opening daily, in order more effectively to reach the ulcerated colon. The quinine treatment was only moderately effective and was abandoned in a few years.

In 1911 a great advance in therapy was made. Vedder³ that year in Manila discovered that the amoebae were readily destroyed by emetine. The following year, 1912, Leonard Rogers⁴ demonstrated the great efficiency of emetine hydrochloride in the treatment of intestinal and hepatic amoebiasis in India. He found it not only most efficient in relieving the intestinal features but also in cutting short the symptoms of amoebic hepatitis. It is well to remember that even before 1911 ipecac, by oral administration, had already been used with very considerable success, but this procedure was objectionable owing to the nausea and vomiting likely to be produced.

Since Vedder's important contribution, treatment with emetine hydrochloride has come into general use as one of the measures for the treatment of amoebiasis and has been most satisfactory. The drug is often almost as specific as is quinine in malaria. Whereas various directions for its use are given, a very satisfactory method is to give 21 mg (1/3 gr) hypodermatically three times a day for ten days. This was the procedure carried out in this patient, with great benefit particularly to the liver manifestations. Owing to the tendency of amoebic dysentery to relapse it is wise to give one or two other courses after intervals of seven to ten days. In an active dysen-

tery with numerous amoebae in the stools, the diarrhoea or bloody stools promptly cease and the amoebae rapidly disappear. Manson-Bahr states that emetine is a much more effective amoebacide in metastatic amoebic lesions than it is in amoebic dysentery, and, therefore, is most efficacious in the hepatic complications, especially if used in the early stages.

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they have the power of penetrating the walls of the ulcers, with an amoebacidal effect on the parasites embedded in the tissues. Being arsenical preparations and knowing the damage that the various salvarsan remedies sometimes produce in the liver, it is a question whether it is wise to use them in suspected amoebic abscesses of the liver or amoebic hepatitis.

From personal experience I am firmly convinced that amoebic abscess of the liver in recent years has been much less frequent since the introduction of emetine hydrochloride in the treatment of amoebiasis. In 1903 I⁵ analysed the first 120 cases of amoebiasis that occurred in the Johns Hopkins Hospital since its opening fourteen years before. With one exception, all these cases were cases of intestinal amoebiasis. The exception was one in which Flexner found amoebae in an abscess in the floor of the mouth in one of Dr. Halsted's surgical cases. Among the other 119 cases hepatic abscesses were present in 27, or 22.6 per cent. Nine of these ruptured into the right lung, producing hepatopulmonary abscesses with the expectoration of anchovy sauce sputum, two ruptured into the right pleural cavity, three opened into the inferior vena cava. Of eighteen liver abscess cases that came to autopsy, there were ten cases with a single large abscess in the upper part of the right lobe, and there were eight with multiple abscesses.

In recent years there has been a growing tendency on the part of surgeons and medical men not to resort to surgical procedures in opening a solitary amoebic abscess of the liver. Some now advise the draining of the abscess by trochar at the proper point and the introduction at the same time of a certain amount of a solution of emetine hydrochloride into the cavity. The claim is made that this procedure gives a lower mortality than does surgical drainage.

In the present case we are quite certain that the patient did not have an amoebic abscess of the liver but an amoebic hepatitis, which promptly yielded to the administration of emetine hydrochloride and yacon.

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2 Meningococcus Meningitis

By WILLIAM S TILLETT, M D
Visiting Physician

and

HAMILTON SOUTHWORTH, M D
Assistant Resident Physician

CASE presented by Dr Hamilton Southworth

This patient is an eighteen year old colored boy whose family history and past history are irrelevant to his present condition. For three to four days preceding his admission he had a mild head cold. The night before admission he had a sudden nosebleed followed, almost at once, by severe headache and pain in the right side of the chest on respiration. He had two shaking chills and afterwards became feverish and drowsy. The next day all his symptoms had increased and he was sent to the hospital as a case of incipient lobar pneumonia.

On admission, the temperature was 102 0°, the pulse 104, respiration 24, and blood pressure systolic 104, diastolic 70. Physical examination revealed an acutely ill but well nourished boy who was drowsy but oriented. He lay on his side with his knees drawn up and his head thrown slightly back. Breathing was not labored but there was obvious splinting of the right side of the thorax. He was generally hyperesthetic with particular sensitiveness over the lower thorax on the right. The neck was slightly stiff and Kernig's sign was suggestively positive. No petechiae or purpuric spots were seen. The eyes, ears and throat did not appear abnormal. Except for suppression of breath sounds over the right lower lobe the lungs seemed clear. No abnormalities of the heart and abdomen were made out. No abnormal reflexes were elicited.

Examination of the blood showed a leukocytosis of 33,900 with a shift to the left in the neutrophil series. The urine was clear. The blood Wassermann negative. Blood culture remained sterile. A lumbar puncture was performed and faintly opalescent fluid obtained under apparently normal pressure. The Pandy was negative and

but 21 cells were found, 19 of them polymorphonuclears. A tube of the fluid proved sterile on culture.

The patient ran an irregular fever up to 103° and remained a diagnostic puzzle. No definite signs of pneumonia appeared. On the sixth day of disease a second lumbar puncture revealed 32 cells, 26 of them polymorphonuclears. On the eighth day, however, the fluid from a third tap contained 4,100 cells and meningococci were isolated by culture. It therefore became apparent that the patient had entered with an acute meningococcal infection, which did not become a typical meningitis till a week later.

He was immediately treated with concentrated meningococcus antiserum obtained from the New York State Laboratories, and received at six hourly intervals a total of nine intraspinal treatments, the first four of which were accompanied by intravenous injections of the same material. At each lumbar puncture the spinal fluid was drained as completely as possible before the serum was introduced. By the seventh tap, or thirty-six hours after treatment was begun, the spinal fluid culture had become negative. His recovery was uneventful save for a mild urticaria due to serum sickness.

REMARKS BY DR. WILLIAM S. TILLETT

In the history and clinical course of the patient with acute meningococcus infection, including meningitis, about whom you have just heard, there are several findings which merit comment. It is noteworthy that the illness began as an acute respiratory infection, and that he was admitted as a possible case of pneumonia, and that the diagnosis was problematical even after the patient had been on the ward several days. That the upper respiratory tract is the usual portal of entry of meningococcus infection is generally accepted and one of the interesting points is that respiratory symptomatology without definite physical findings referable to the respiratory tract may endure for days or even weeks before the meningitis is manifest. A considerable number of the patients which we have seen in the past two years gave a history of an antecedent respiratory illness prior to the development of usual symptoms of meningitis. They often remained at home during this period but sometimes were admitted to the hospital. I recall one patient who was on the ward for two days with an unsatisfactory diagnosis of influenza. During this period

there was no stiffness of neck or positive Kernig's sign or other evidence suggesting meningitis. She probably did not have meningitis at that time. She suddenly developed the signs of it, however, and spinal fluid, obtained by lumbar puncture, contained many leukocytes and meningococci.

At times of epidemics of meningitis—this region of the country has been having an increased number of cases for the past few years—it is necessary to bear in mind that some of the acute upper respiratory diseases, particularly of February to April, may be the beginning of meningitis or even may be abortive meningococcus infection. The latter condition is mild in degree but is probably of great significance in the epidemiology of the spread of the disease.

Interpreting by hindsight the course in the patient just presented one notes that on admission, at a time when toxicity was not great and physical findings were meagre that the leukocytes in the blood numbered 33,900. The hyperleukocytosis which may accompany meningococcus infections is well known.

Although the patient under consideration did have signs at admission sufficiently suggestive to warrant a lumbar puncture, the fluid contained only 21 cells and no bacteria could be demonstrated, from the second lumbar puncture done four days later the fluid was unchanged. The signs and symptoms continued to point to central nervous system disease, and brain abscess or subdural abscess were given serious consideration. Although there was no definite change in the patient's condition the spinal fluid was found three days later to contain 4,000 leukocytes and meningococci.

The patient might be considered an instance of atypical meningococcus meningitis but the clinical course also emphasizes the fact that meningococcus infection may be obscure and our recent experience has taught us that variability in manifestations may occur even with an acute infection so well defined as epidemic meningitis.

The opportunity has been afforded us during recent years to observe and treat a larger number of cases than usual. In addition to the usual evidences of cerebrospinal infection, extrameningeal manifestations have occurred in approximately 75 per cent of the cases.

Purpura, so characteristic of acute meningococcus infection was noted in approximately 50 per cent of the cases and was much more

frequent in those having bacteremia than in those without demonstrable blood stream infection

Purulent arthritis, a metastatic manifestation, occurred in one-third of the patients. It never became chronic and complete recovery followed within a few weeks after the active disease subsided.

Ocular inflammation occurred in about 15 per cent of the cases, either as conjunctivitis alone or in association with involvement of other ocular tissues. Vitreous abscess of one eye occurred in four patients and led to permanent blindness in the affected eye.

Epididymitis occurred in three patients. The infection subsided uneventfully.

Bilateral destruction of the end organs of hearing occurred in three patients and resulted in complete and permanent deafness.

Forty-five per cent of the cases had bacteremia demonstrable by blood culture.

Serum was administered both intravenously and intraspinally at frequent intervals, 20 cc of uncentrated serum and 10 cc of concentrated material were usually given per dose by each route of injection (the amount given intraspinally being always a few cc less than the quantity of spinal fluid removed). The injections were repeated every six hours. Usually two to three injections intravenously were effective in controlling the bacteremia. After the first twenty-four hours, the subsequent intraspinal treatment was determined by the condition of the patient and the character of the spinal fluid, particularly the total cell count. When improvement was progressively favorable it seemed desirable to prolong to twelve or twenty-four hours the intraspinal treatments or stop the procedure in order to avoid the disadvantages of over treatment. Both concentrated and uncentrated sera seemed equally effective. The number of cases treated with each is too small to afford comparison.

Concerning the condition of the patient, the factors that were considered helpful in evaluating improvement consisted in clearing of delirium or restlessness, decrease or disappearance of hyperesthesia and headache, and cooperation in taking food and fluids. The course of the temperature was often not a reliable index of favorable progress or the reverse. In some instances, patients who were desperately ill showed very little febrile reaction. In others wide daily swings in

the degree of fever undoubtedly were influenced by reaction to serum therapy as well as to the active disease itself

One of the most helpful procedures in estimating the course of the infection consisted in determining changes in the total cell count of the spinal fluid. When the number of cells progressively decreased, it usually indicated that the infection was subsiding. Often after the first injection or two of serum the count sharply increased. This did not persist, however, and when the number of cells was found to be declining by several thousand in samples of fluid obtained on successive punctures, the interval between punctures was prolonged, or even stopped for several days.

In some instances the decrease in the number of bacteria in successive samples of spinal fluid was definite enough to be indicative of a subsiding infection. Since, however, meningococci were, in many cases, difficult to find even in the acute stages of infection, changes in their number often could not be measured. Consequently, the prompt examination of stained smears of the several specimens of spinal fluid for bacteria did not regularly assist in evaluating the course of the infection.

Special attention has been directed toward the cause of death in the fatal cases. This study, now in progress is incomplete. However, the analysis suggests that there may be special factors peculiar to meningococcus infection which are not explicable on the basis of progressively increasing bacterial infection leading to death. The reason for this consideration of the problem is based upon the fact that in some of the intensively treated patients who lived several days but finally died, blood and spinal fluid cultures were eventually sterile both ante and postmortem and the degree of meningitis found at autopsy was minimal and only microscopic. In seeking elsewhere for pathological anatomical changes, bilateral massive hemorrhages of the adrenals were noted in four of the fatal cases. "Adrenal apoplexy" and a so-called "Waterhouse-Fredrichson Syndrome" have been described in the literature which are characterized by sudden onset, short duration, sudden death, and hemorrhages into the adrenal glands.

The accumulating articles indicate that the meningococcus may be an important pathogenic bacterium in evoking this type of illness.

It should also be noted that in some of the fulminating cases

gross pathological anatomical changes were not noted in the adrenals, although the general course of the disease was similar to that occurring in those with massive adrenal hemorrhages. One should bear in mind, therefore, that it may be necessary to seek elsewhere than the adrenal glands for the critical bodily functions which appear, in some instances, to be so vulnerable to acute meningococcus infection.

Our interest in these latter considerations concerns the possible improvement in therapy—especially of the extremely severe cases—which might derive from an understanding of the underlying pathological physiology.

3. Multiple Polyposis and Pyelonephritis

By WARFIELD T LONGCOPE, M D
Physician in Charge

and

M RICHARD WHITEHILL, M D
Assistant Resident Physician

CASE presented by Dr M Richard Whitehill

This patient, a sixteen year old, white, single school girl, was admitted to the medical service of the Johns Hopkins Hospital September 27, 1936. Her father died at the age of twenty-nine of carcinoma of the rectum after many previous attacks of diarrhoea. A sister died at twelve of some acute abdominal condition. The patient's past history contains nothing suggestive of previous renal disease. However, she has never been robust. As long as she can recall she has been pale. For seven or eight years she had attacks of abdominal cramps and diarrhoea, occurring every two to three months and lasting one to two weeks. During these attacks she was ill enough to take to bed, had five to seven watery stools a day, and usually developed fever. Stools on one or two occasions were described as black, were never seen to contain red blood, pus or mucus. Between attacks her bowels moved two to four times a day, and the cramps occurred only occasionally. The present illness was ushered in by a particularly severe attack of cramps and diarrhoea beginning nine days before admission to the hospital. A week before admission she developed a pounding headache and her eyes became puffy. The next day she was unable to get on her shoes because of swelling of the feet. Finally, because the cramps were so bad, and because her local physician noted swelling of the face, fingers and feet she was sent to the hospital. Nausea and vomiting did not occur. Urine appeared normal in color. She felt that her temperature had been elevated.

On admission her temperature was 100.6, pulse 116, respirations 18, blood pressure, systolic 120, diastolic 85 (both arms). She was an acutely ill very pale young white girl. There was slight firm gen-

eralized edema, accentuated about the face, hands and feet. There was no evidence of an upper respiratory infection or of any focus of infection in the nose or throat. There was no respiratory difficulty. The lungs were clear to percussion and auscultation. The urea clearance was only 25 per cent of the normal standard clearance. The plasma proteins were 4.81 Gm. per cent with an A/G ratio of 60/40. The albuminuria rapidly decreased until after five days it was very slight and remained so. The urinary sediment likewise changed to show rare red cells and casts, many white blood cells. Most of the casts were leukocytic.

The edema disappeared after about five days in the hospital. However, the child became worse. She had three to seven loose bowel movements a day, suffered from severe generalized abdominal cramps, ran a febrile course with the rectal temperature fluctuating from 100° to 103°. Stools contained occult blood, no pus or amoeba. Blood cultures were sterile. Agglutinations against the typhoid, dysentery and suisstifer groups were negative. Agglutinations against *Brucella abortus* were positive to a dilution of 1/160. Her abdomen became slightly distended and quite tender and resistant in the right upper quadrant. Finally, after this course continued over a week, it was suggested that she might have multiple polyposis of the colon. A rectal examination revealed numerous pea sized nodules projecting from the mucosa. By proctoscopic examination many small polypi were seen extending from the rectum to the sigmoid and the mucosa bled on the gentlest trauma. Double contrast barium enema showed what were interpreted as polypi throughout the entire colon.

Treatment consisted of two transfusions of 500 cc of citrated blood each, bismuth subcarbonate, paregoric, ferrous sulphate and sedatives. A low residue, high protein diet was given. Diarrhoea and cramps gradually subsided over ten days. The stools remained normal after the first week. Consequently, after two weeks in the hospital she was asymptomatic and afebrile. Blood counts immediately improved after the transfusions, became normal after three weeks. Renal function improved so that the nonprotein nitrogen of the blood was 34 mg per cent, the phenolsulphonephthalein excretion 72 per cent in two hours, the urea clearance 60 per cent of the normal standard clearance after a little over two weeks.

The urine, however, continued to show a slight trace of albumin and many leukocytes. Urine cultures were positive on three occasions for *Bacillus coli*. Over four days she was given by mouth a total of 18 Gm. of ammonium chloride in enteric coated capsules. The urine then was acid to methyl red, and she was given ammonium mandelate, 12 Gm. daily for five days. On the second day of mandelate therapy, a urine culture was sterile except for a light growth of *staphylococcus albus*, most probably a contaminant. One other culture contained the same organism, and three others were entirely sterile. After the urine became sterile, the albumen and white cells gradually decreased and finally disappeared entirely. The child has been transferred to the surgical service for ileostomy preparatory to colectomy. A biopsy of one of the rectal polypi showed numerous mitotic figures.

The case is presented as one of familial multiple polyposis of the colon, and acute pyelonephritis which we believe occurred by hematogenous spread of *Bacillus coli* from the intestines to the kidneys. The urine was rendered sterile by treatment with ammonium mandelate.

REMARKS BY DR. WARFIELD T. LONGCOPE

This patient confronts us with two interesting problems which are totally different, and yet the presence of one condition has, we believe, been responsible directly for the precipitate occurrence of the other. In the first place this young woman presents the symptoms, the physical signs, the changes by proctoscopic examination and the radiographic picture of multiple polyposis. This disease is comparatively rare, occurs generally in families, gives rise to attacks of pain such as you have heard described and from the therapeutic point of view is extremely difficult to manage. From the history and the subsequent events we may assume that, following one of the acute attacks of pain, often associated with an infection of one of the polyps, there was a sudden onset of acute pyonephritis leading to very severe renal insufficiency. The cause of the pyonephritis has been proven to be *Bacillus coli* which in all probability in this patient reached the kidney by the hematogenous route. The occurrence of the acute pyonephritis under such circumstances has absorbed, temporarily, our attention for when such an infection persists it frequently leads

to a chronic pyelonephritis with all the serious results that attend upon the progression of that disease

There has been much discussion in the literature as to the origin of acute pyelonephritis in the adult. It is held by many that the disease, even when it occurs without obvious obstruction to the urinary tract, arises as an ascending infection of the ureters, but Bugbee, Choun, Wilson and Schloss, as well as Dunlop and Dick all hold the point of view that in the infant so-called acute pyelitis results from hematogenous infection of the kidneys and starts as multiple minute abscesses scattered through the parenchyma of the organ. It is very difficult to determine in the adult, during the advanced stage of chronic pyelonephritis, where the infection begins for with the constant elimination of pus in the urine secondary inflammation of the ureters, particularly as they pass through the muscular walls of the urinary bladder, is likely to occur and at the final examination it is almost impossible to determine whether these points of narrowing and inflammation preceded the involvement of the kidneys or resulted as a complication. It seems clear, however, that in this young adult the process must have started as a bilateral hematogenous infection producing not only symptoms and signs of acute nephritis but the changes which accompany severe renal insufficiency. Fortunately the acute phase of the illness subsided rather rapidly, for within three weeks of the onset of her illness she was much improved clinically, the edema had disappeared, the albuminuria and hematuria had diminished and the function of the kidneys was almost normal. The pyuria and cylindruria persisted, however, unchanged. Cultures from the urine continued to show *Bacillus coli*.

On account of the possibility that this condition might continue and lead to a chronic pyelonephritis, it was highly desirable to rid the patient of the infection of the urinary tract if such a thing were possible. To this end a drug introduced comparatively recently was employed. This drug is Ammonium Mandelate, the use of which is the outcome of the original studies of Dr. Helmholtz upon the therapeutic effect of a ketogenic diet upon urinary infections. In a series of interesting observations, Fuller found that the active substance which is excreted in the urine under these conditions is Beta-oxybutyric acid and, since this drug is so rapidly oxidized that it cannot be used by mouth, a search was made to find a substitute

This was discovered by Rosenheim in 1935 who found that mandelic acid compared favorably in its bacteriostatic action with Beta-oxybutyric acid. This chemical can be administered by mouth, is non-toxic for man, and in the presence of an acid urine renders the urine bacteriostatic. Since these earlier observations there have been many reports concerning the therapeutic effects of mandelic acid upon infections of the urinary tract due to *Bacillus coli*. The reports in general have been favorable. It is necessary, in order that the drug be effective, that the urine be rendered acid and brought to a pH of at least 5.5. This can usually be accomplished by giving the patient ammonium chloride for two or three days before starting the administration of the ammonium salt of mandelic acid. To maintain the required acidity of the urine ammonium mandelate is given in doses of approximately 12 Gm. a day for a period of about five days.

In patients with any degree of renal insufficiency there is always the danger that a severe acidosis may develop, and for this reason repeated determinations of the CO₂ combining power of the serum must be made during the preliminary administration of ammonium chloride and during the course of ammonium mandelate. If acidosis appears the drug must be stopped immediately.

In this patient on the third day after the administration of ammonium mandelate the urine was sterile and, following the course, pyuria and cylindruria rapidly disappeared and the albuminuria and hematuria ceased entirely. For several days now the urine has been normal and cultures have shown no growth of bacteria. It often happens, after a single course of ammonium mandelate, that there are exacerbations of the infection and consequently it may be necessary to give repeated courses of the drug to this patient before the infection is completely eliminated, but our hope is that this may be accomplished and that she may be completely cured of the infection of the kidneys which might readily endanger her life in the future and certainly would interfere materially with any procedures one might desire to institute in order to relieve by radical measures the multiple polyposis of the colon.

4 Friedlander's Pneumonia

By CHARLES R AUSTRIAN, M D
Assistant Visiting Physician

and

A M HARVEY, M D
Assistant Resident Physician

CASE presented by Dr A M Harvey

This patient, a fifty-eight year old colored saloon helper, was admitted to the hospital on November 9, 1936 complaining of pain in the right side of the chest, weakness, and loss of weight. The patient had always been in good health prior to the onset of this illness. He has been subject to one or two mild head colds each winter, but they were never accompanied by fever or cough. Since his employment in a saloon two years previously he has been a moderate user of whiskey. There has been no exposure to poisonous fumes, asbestos, or to dust.

The patient felt perfectly well until three weeks before his entry into the hospital at which time he caught a heavy cold. Nasal obstruction persisted, and he developed a cough which was productive of small amounts of whitish, mucoid sputum. He grew progressively weaker, anorexia ensued, and he began to lose weight. Two weeks after the onset of his illness the cold went into his chest, and a feeling of tightness and sharp pain was noticeable over the lower portion of the right side of the thorax whenever he coughed. Shortness of breath developed and slowly progressed in severity. During the week before his first examination he had several severe night sweats. There was never a chill, pain associated with respiration, or blood-tinged sputum.

On admission the temperature was 102° F, pulse rate 95, and respiratory rate 22 per minute. The patient had obviously lost a good deal of weight and appeared chronically ill. There was marked pallor of the mucous membranes, but no cyanosis or jaundice was visible. He was short in stature, with small extremities, a prominent frog-like abdomen, and marked flaring of the lower costal margins. The trachea was deviated to the right. The movement of the chest was

limited but symmetrical on the two sides. There was marked dullness to percussion over the region occupied by the right lower and middle lobes. The breath sounds were distant and bronchial in character in these areas, and during inspiration many crepitant and consonating râles were audible. Similar signs were present over a small area just below the angle of the scapula on the left side, and in addition a loud pleural friction rub was heard in this region. The descent of the lung bases was limited. The heart was not enlarged or shifted in position. The sounds were of good quality and no murmurs were present. The blood pressure was normal. The liver and spleen could not be palpated. No clubbing of the fingers was noted, and there was no peripheral edema.

Laboratory Examinations —

Blood Red blood cell count, 2,85 million, hemoglobin, 9.4 gr (65 per cent), white blood cell count, 20,900, differential count juvenile polymorphonuclear cells 11 per cent, segmented polymorphonuclear cells 80 per cent, lymphocytes 9 per cent

Urine Dark amber in color, clear, specific gravity 1.020, trace of albumin, sugar, acetone, diacetic negative, urobilin strongly positive

Nonprotein-Nitrogen, Van den Bergh, and carbon dioxide combining power were normal

The *Wassermann reaction* was strongly positive

The *sputum* was thick, tenacious, quite stringy, greyish in color, but contained no blood. Culture showed a predominant growth of Friedlander's bacillus and a moderate growth of pneumococcus type VIII. No spirochetes or tubercle bacilli were found after careful search.

There was no growth in the *blood cultures*

Roentgenograms of the chest were reported as area of partial consolidation in the right lower and middle lobes. Small patch of consolidation in the right lung.

Course in the Hospital — The patient is now in the eighth week of his illness. There has been a persistent, intermittent type of fever, the temperature varying from 99.6° F per rectum to 102.3° each day. There has been no diminution in the extent of the process in the lungs. No cavity formation has taken place, and no accumulations of fluid have formed. Symptomatically the patient is greatly improved and

during the past two weeks has gained five pounds in weight. The white blood cell count has gradually returned to a normal level, and the urobilin has disappeared from the urine. Cultures of the sputum continue to show Friedlander's bacillus as the predominant organism.

REMARKS BY DR. CHARLES R. AUSTRIAN

This patient, at the time he was admitted to the hospital, presented the symptoms and the signs of an infection of his lower respiratory tract. Examination localized the pathological process in the lower and middle lobes of his right lung, where there were evidences of incomplete pulmonary consolidation and of fibrinous pleurisy, together with suggestive signs of encapsulated fluid in the fissure between the middle and lower lobes.

During the period that he has been under observation, the signs of parenchymal involvement of the right lung changed little, but from day to day a pleural friction rub was palpable and audible over the affected areas and localized signs of involvement in the base of the left lung appeared.

The clinical picture presented could have been due to delayed resolution or to organization of an ordinary pneumococcal infection, a condition not unusual in a syphilitic negro, to a so-called chronic non-tuberculous basal infection, to bronchiectasis with pulmonary suppuration, to multiple abscesses with encapsulated interlobar empyema and compression of the adjacent lung, to a tumor, to basal tuberculosis, or to a mycotic infection.

The differential diagnosis of these several conditions need not be discussed at length in this brief clinic. Suffice it to say that the initial examinations of the sputum did not show the presence of tubercle bacilli or of fungi, nor did roentgenography disclose shadows suggesting neoplasm or abscess. The clinical acumen of Dr. Harvey, Assistant Resident on the Ward, led to the search for and demonstration of Friedlander's bacillus in the sputum in such numbers as to incriminate it as the etiological agent in the case. Cultures of the sputum demonstrated that organism and a pneumococcus Type VIII, but a culture of the blood was sterile. The charts, as you see, indicate the persistence of a low grade pyrexia up to 101.5° , a relatively low pulse and a moderate leukocytosis. These roentgen films of the chest show essentially unchanged evidence of infiltration of the lower and

middle lobes of the right lung, without signs of excavation and a small area of infiltration in the lower lobe of the left lung. There is visible, likewise, in the lateral view, evidence of fluid in the fissure between the middle and lower lobe of the right lung. The last film indicates a displacement of this fissure downward as if the volume of the lower lobe were decreased but no evidence of cavity in the lobe. It is clear from the evidence presented that the illness of the patient is attributable to a subacute pneumococcal process with pleurisy due to Friedlander's bacillus.

This organism, designated sometimes *bacillus mucosus capsulatus*, was discovered by Friedlander in 1882 and was believed by him to be the usual cause of lobar pneumonia but when Fraenkel described the pneumococcus two years later, Friedlander's organism lost caste and by many came to be considered solely as a secondary invader and by others as a primary agent in only from 5 to 10 per cent of the cases of pneumonia. That Friedlander's bacillus is potentially a primary menace to man is evidenced by experimental as well as by clinical facts. Branch and Stillman demonstrated that when mice are sprayed nasally with it, they develop an interstitial lobular pneumonia with sepsis. Webster described a spontaneous epidemic of pneumonia in a colony of mice due to a Friedlander-like bacillus. Julianelle described smooth (S) and rough (R) forms of the bacillus and demonstrated specific immunological reactions for three types of the organism, and Avery with his co-workers, isolated from the bacillus a specific nitrogen-free polysaccharide. Moreover, Zander described an epidemic of Friedlander bacillus pneumonia in Germany, and finally, the demonstration of the organism in the sputum, blood and lungs of human patients attests to its clinical importance.

As you know, the bacterium is a short, broad bacillus with rounded ends almost like a coccus in appearance, gram negative, non-motile and enveloped by a large, easily stained capsule. It forms large, moist, translucent, mucoid colonies when grown on solid media, has characteristic fermentation reactions in media containing sugars and gives rise to specific immunological reactions in infected hosts.

The pathological changes are suggestive though not entirely characteristic. The involved lung shows areas of consolidation with intervening patches of normal tissue—a confluent, lobular or pseudolobular rather than a true lobar consolidation—and frequently a coexisting

pleurisy. The affected lung looks voluminous and the marbled, cut surface is mottled brown or grayish and generally exudes a profuse, slimy exudate. Frequently, multiple, thin-walled abscesses are present and between these cavities are irregular areas of air-containing tissue. Microscopic examination shows inflammation of the interstitial tissue and alveoli filled with polymorphonuclear leukocytes, degenerated lymphocytes, alveolar epithelium, typical bacilli (both intra- and extra-cellular) but less fibrin than is seen usually in pneumococcus pneumonia.

Friedlander bacillus pneumonia is chiefly a disease of late adult life and has a very variable clinical course. You are all familiar with the more usual, briefly enduring, acute type of the disease. The onset may be abrupt and the clinical picture confused with that of pneumococcus pneumonia. Though chills occur less often, herpes develops less frequently and haemoptysis more regularly, though defervescence by lysis is more usual and tachycardia and leukocytosis are less marked, none of these features is distinctively diagnostic nor is the expectoration of copious, bloody, mucoid sputum more than suggestive unless it is laden with the specific bacillus. Frequently there develops a clinical picture like that which was presented by the interstitial pneumonias that occurred during the pandemic of influenza in 1918-19. Cyanosis and toxemia are profound, weakness, drowsiness, coma, evidence of circulatory and of respiratory failure develop rapidly and death may occur within twenty-four to forty-eight hours. The mortality of the acute disease is high and there is but one recorded recovery of a patient with sepsis due to this organism.

The chronic type of pulmonary infection with Friedlander bacillus, illustrated by the patient before you, is less generally known. Admirable descriptions of it have been published by Belk, by Collins and Kornblum and by Collins. The onset of this type may be like that of an ordinary lobular or lobar pneumonia. If the somewhat suggestive characteristics enumerated a moment since are wanting, differential diagnosis must await the clinical course, the bacteriological studies and the evolution of the disease. In such event, physical examination from day to day will indicate the extreme indolence of the pulmonary lesion, examination of the blood may show a relatively slight leukocytosis, the sputum may be copious and stringy, there may be relative bradycardia and defervescence may occur by

lysis Friedlander's bacillus may be demonstrated in cultures of the blood or in material obtained by puncture of the lung and the roentgenogram may show characteristic changes According to Collins, serial roentgenographs during the evolution of the disease show at its onset shadows of bronchopneumonia that do not differ essentially from those due to other pathogenic agents These coalesce very rapidly to give an appearance like lobar pneumonia except that the shadows do not appear to be as homogeneous, are not usually limited to one lobe and are more intense at the periphery of the lung Within a variable period of time—slowly in cases that become chronic—evidences of pulmonary excavation appear, leading to a more or less characteristic appearance presented by multiple, very thin-walled cavities According to Westermark, the very thin walls of these abscesses is distinctive Death occurs often at this stage of the disease, but if it does not, and recovery ensues, evidences of fibrosis with cavities are shown

The course of the malady may be extremely protracted, with minor clinical manifestations alternating with acute exacerbations of symptoms and signs The clinical picture may be confused readily with that of pulmonary tuberculosis from which differentiation is made first by having the condition in mind, secondly, by the failure to demonstrate tubercle bacilli in sputum examined properly and frequently, thirdly, by the tendency of the changes to occur in the lower lobes, fourthly, by roentgenographic evidence, and finally, by the demonstration of Friedlander bacillus in sputum, blood or material obtained by puncture of the lung

The treatment of the acute form of this disease is entirely symptomatic for no specific measures are available They consist chiefly in combating anorexia and toxemia, in relieving pain and lessening but not suppressing cough, in promoting elimination and in stimulating circulation and respiration The therapy of the chronic variety is likewise palliative and supportive—rest, general tonic measures, postural drainage, relief of pain and of cough if it is harassing Vaccines have no proved merit nor have other forms of specific treatment proved beneficial In isolated instances of extensive suppuration or of large abscess-formation, surgical intervention has been recommended and has been practiced successfully

It is not unlikely that instances of chronic pulmonary infections with Friedlander's bacillus occur more frequently than is generally

thought. They present a clinical state so like that caused by chronic pulmonary tuberculosis, that if tubercle bacilli can not be demonstrated in the sputum of a suspected instance of the latter disease, Friedlander's bacillus should be included in the group of pathogens sought for.

5 Diabetes Mellitus Treated with Protamine Zinc Insulin

By GEORGE A HARROP, JR, M D

Visiting Physician

and

M RICHARD WHITEHILL, M D

Assistant Resident Physician

PROTAMINE insulin was introduced in Denmark by Hagadorn and his associates about two years ago. It is a combination of insulin with a protein-like compound, "protamine", which is derived from the sperm of certain species of fish. The cloudy suspension, which is formed at a properly adjusted acidity, is broken down and absorbed more slowly from the tissues after subcutaneous injections than is ordinary insulin. Therefore the physiological effect is slower and more lasting. During the past summer a further improvement was made by the addition of zinc in very small quantities to the protamine insulin. This compound, known as protamine zinc insulin, is now dispensed exclusively, the manufacture of the original protamine insulin having been given up. The addition of the zinc makes the action smoother and more effective and improves the stability of the compound.

We have had about forty-five diabetic patients under treatment with this new form of insulin therapy during the past year and a half, and we will present the records of four of them to illustrate both successful and unsuccessful results of treatment.

CASE I.—This patient is a twenty-eight year old single, white, male. He has been a known diabetic for three and a half years. His first admission was in 1934 because of moderate acidosis. He was discharged sugar free on a diet of C 120, P 70, F 140,* insulin 30-0-20-0 †

* "C" represents grams of carbohydrate, "P", grams of protein, and "F" grams of fat in the daily diet.

† The insulin dosage is given for convenience in this form, and here means that 30 units were given before breakfast, none at lunch time, 20 units at supper, and none in the late evening.

On that regime an all-day sugar curve was 145, 50- 95- 60 * During the next three years he was followed in the dispensary Because of a few mild reactions, the insulin was reduced to 20-0-18-0 Generally the urine contained no sugar In August, 1936, the use of protamine zinc insulin was begun On 14 units of protamine before breakfast, and the same diet divided as to the carbohydrate content of the meals as 1/5, 2/5, 2/5, an all-day sugar curve was 81, 101, 77, 112 Recently he has been maintained almost sugar free with 16 units of protamine and the diet carbohydrate divided in thirds

This patient represents an excellent response to protamine therapy He is a young man with mild diabetes His total insulin requirement and the number of injections have been reduced The blood sugar values are at physiological levels throughout the day

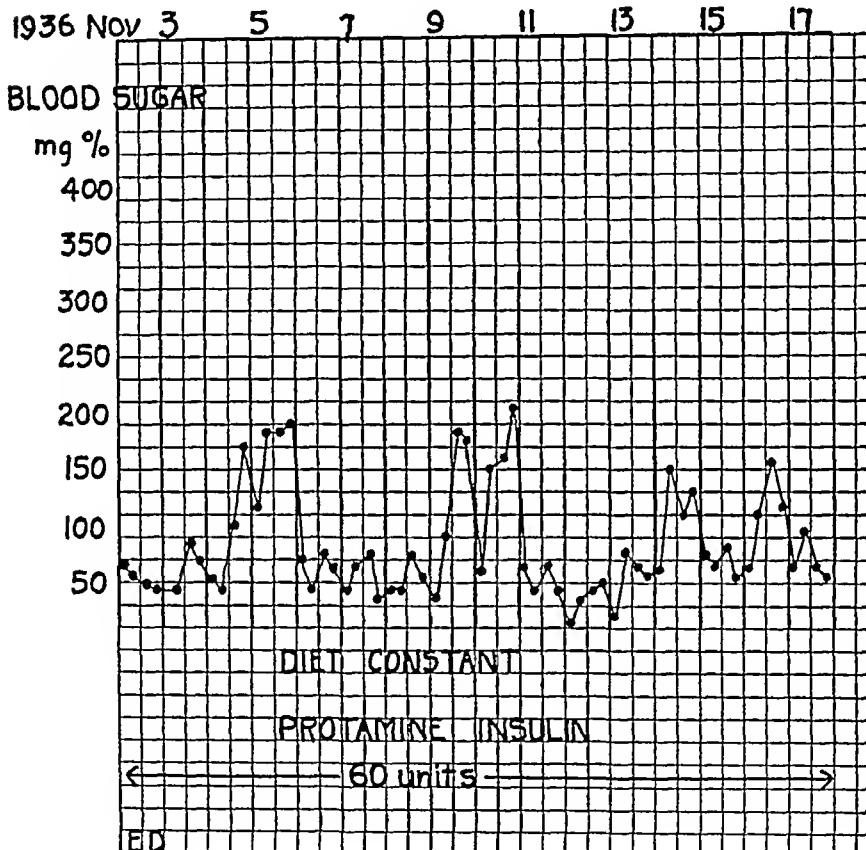
CASE II.—This patient is a twenty-six year old white, single, domestic, who has had thirty-three admissions to the Johns Hopkins Hospital since 1925 All the admissions were for diabetic regulation or for infections Since 1926, her liver from time to time has been found enlarged, and early in the course of the disease there were attacks of right upper quadrant pain associated with apparent increase in the size of the liver Until a few years ago almost every respiratory infection was associated with acidosis Regulation for a number of years was very difficult, in part, because of frequent infections and poor cooperation However, in recent years she has been fairly well controlled with large doses of insulin On a diet of C150, P50, F100 and insulin dosage of 40-15-20-20, there was slight glycosuria, and an all-day blood sugar curve was 220,119, 91, 98 Protamine insulin was commenced March 25, 1936 Shortly after, she began having attacks of diarrhoea which were not satisfactorily explained, and which added to the difficulty of regulation Various combinations of protamine insulin alone and protamine with regular insulin were attempted On 40 units of protamine in the morning and 35 units of protamine at night an all-day sugar curve was 63, 135, 215, 238 and 35 On 20-6-12 units of regular insulin and 12 units of protamine at 10 00 p m the curve was 200, 145, 164, 87 and this regime seemed

* The blood sugar readings represent the values obtained on samples taken before breakfast, lunch, supper, and in the late evening respectively, and given as milligrams per cent

the most satisfactory. With it there was moderate glycosuria. It does indicate some improvement over her previous regulation.

This represents a case of severe diabetes in which complete substitution of protamine for regular insulin was impossible, but who was somewhat improved by the substitution of a single dose.

CHART 1



CASE III.—This patient is a nineteen year old single, white girl, and a known diabetic since 1933. It is interesting that her sister has two children who are diabetics, and that the onset of the patient's symptoms was two months after an attack of catarrhal jaundice. Her disease is moderately severe and regulation on ordinary insulin was only fairly successful. Cooperation at first was poor, but has now improved. Acidosis developed quickly with infections. On

a diet of C 130, P 70, F 90, insulin 38-0-28-0, the all-day sugar curve was 263, 139, 194, 52, and moderate glycosuria was present. From November 2, 1935, she has been receiving protamine and protamine zinc insulin. For the first month of protamine therapy, capillary blood sugar estimations were made four times daily. On 50 to 60 units of protamine before breakfast blood sugar values showed an irregular cyclical variation (See chart 1). For three or four days there were values of 50-80 mg per cent and then for no apparent reason values from 80-150 mg per cent occurred. There were occasional mild reactions. It was decided that more satisfactory regulation could be attained by combining the use of regular insulin with protamine insulin. For about two months she has been receiving protamine insulin 25 units and regular insulin 12 units in separate injections before breakfast. Glycosuria has been slight, reactions rare, and subjectively she has been well. Blood sugar estimations before lunch have been within physiological levels.

This case is one in which a single large dose of protamine zinc insulin was not satisfactory. With it hypoglycemia and hyperglycemia were present during the same twenty-four hours. By reducing the large dose of protamine and substituting a smaller amount of regular insulin, regulation has been excellent.

CASE IV—This patient is a forty-one year old white, single, graduate nurse with diabetes of about ten years' duration, diabetic retinitis, neuritis and incipient bilateral cataracts. She also had inactive rheumatic heart disease with mitral stenosis and incompetency, and aortic stenosis and incompetency. For about nine years the diabetes was fairly well controlled by private physicians with diet and insulin. About four months before she first entered the Johns Hopkins Hospital she contracted a sinus infection, and rapidly developed acidosis. From then on regulation was very difficult, and was made so, in part, by recurring bouts of diarrhoea. The diarrhoea could not be explained even after fairly exhaustive study. Four doses of regular insulin, totaling 30 units a day, were required for regulation with a diet of C 50, P 60, F 90. This diet was insufficient in caloric content. For four months, regulation was attempted with various combinations of protamine and regular insulin. Of these combinations, the maximal protamine dosage was protamine 25 units before breakfast, regular 8 units before supper, protamine 16 units at 9:00 p.m., while when treated with a preponderance of regular insu-

lin, the maximal dosage of regular insulin was 22-15-12, with 12 units of protamine at 11 00 p m Her diet during protamine regulation was C 130, P 90, F 65 Constant glycosuria, moderate to heavy, with occasional severe hypoglycemic reactions finally made it clear that the use of protamine insulin was not feasible For about three months she has been fairly well regulated without insulin reactions on four daily doses of regular insulin totaling 45 to 60 units There is mild to moderate glycosuria

This is a case of severe diabetes complicated by rheumatic heart disease Despite numerous combinations of protamine and regular insulin, satisfactory regulation was not achieved There was both objective and subjective improvement when regular insulin was resumed

These four patients illustrate the variation which we have seen in therapeutic response to the new medication The first case has undoubtedly shown marked improvement and he represents a group of patients, generally with mild diabetes in which few or no complications have occurred In these successful cases careful cooperation has been secured This we believe essential for satisfactory results The second patient has also been helped, although the effect has been less striking The third patient presents an interesting complication which is of therapeutic importance, namely, the alternation of periods of hypoglycemia with periods of hyperglycemia These cycles are not found to be rare if frequent blood sugar determinations are made It is evident that isolated blood sugar determinations may be misleading If additional insulin had been given to this patient during the period when the blood sugar was found to be high, severe insulin reactions might have resulted during the low blood sugar period which followed

We have observed a number of such severe reactions which differ in some respects from those seen with regular insulin They are especially apt to occur when sufficient insulin is given to prevent the occurrence of hyperglycemia over the entire day The patients usually relapse into these insulin reactions gradually and often are almost unaware of them, although the peculiarities of their behavior may be apparent to the observer Despite treatment by mouth, or even intravenous glucose, symptoms will sometimes persist The absorption of food from the stomach is gravely impaired in conditions of severe and prolonged hypoglycemia, and the ingestion of quickly metabolized

carbohydrate foods cannot surely be relied on to stop the attacks completely. Nervous manifestations are especially marked, and we have had a number of examples of transient hemiplegia and of localized convulsive seizures. Severe headache is experienced for several hours after such an attack. When headache is complained of upon arising in the morning, it is highly suggestive of an abnormally low blood sugar during the preceding night. We have also learned that patients taking protamine insulin who complain of drowsiness or mental dullness may really be suffering from such chronic hypoglycemia. As is well known, the blood sugar level at which clinical insulin reactions occur varies considerably, and we have had numerous instances in which the blood sugar concentration (capillary) has been 60 or less over prolonged periods without evidence of symptoms. The consequences of maintaining the blood sugar for many hours or days consistently below the normal physiological level are not known. Hypoglycemia not due to insulin administration has been found to produce cerebral hemorrhages. The possibility of similar clinical effects must be borne in mind, during the course of treatment with protamine zinc insulin.

In summary the most serious drawback to the use of protamine zinc insulin instead of ordinary insulin in the treatment of some individuals lies in its prolonged and not always predictable action. Care is needed in order to avoid recurrent insulin reactions. Protamine zinc insulin is by no means an innocuous therapeutic agent which can be prescribed with relative disregard of consequences. It is very difficult for patients always to adjust their own insulin dosage in the face of minor variations in their daily routine. For patients who will not submit to a carefully regulated dietary regime we feel that the use of regular insulin is usually safer and more satisfactory. The greatest field of usefulness for protamine zinc insulin, we feel, will probably lie in the treatment of mild or moderately severe diabetes. In these cases, requiring two or three doses of insulin daily, more satisfactory regulation can often be attained by the substitution of a single dose of protamine or of a dose of protamine, combined with regular insulin. In the severe case receiving multiple doses of insulin, the substitution of one or two doses of protamine for regular insulin, at times results in an improvement of the blood sugar level.

6 Subacute Bacterial Endocarditis

By LOUIS HAMMAN, M D
Visiting Physician

and

THOMAS MCP BROWN, M D
Assistant Resident Physician

CASE presented by Dr Thomas MCP Brown

This thirty-one year old white laundry truck driver was admitted to the Johns Hopkins Hospital on November 17, 1936, complaining of a "run down condition"

His family history is unimportant. Between the ages of seven and nine years he had recurrent attacks of swelling of the glands in his neck, however with these attacks he does not recall ever having had tonsillitis or a sore throat. At the age of sixteen he had mild aches and pains in his extremities. He was told that these were "growing pains". The symptoms were never severe enough to confine him to bed. Two years later, at the age of eighteen, his doctor told him that he had a "leaky heart," however for the next twelve years he had no symptoms referable to his heart.

Ten months before admission he noted loss of energy, but he was able to continue with his regular work as a laundry truck driver. There was no increase in dyspnea on exertion at this time, even when he carried heavy bundles of laundry up three flights of stairs. He did notice occasional pains in the joints which persisted for several months. Six months before admission he began to have night sweats, and these have persisted. Nine weeks prior to admission he noticed palpitation of his heart and marked exertional dyspnea, but he continued to work until one week before coming to the hospital, when he was forced to go to bed, because of the increasing severity of his symptoms. His appetite has become poor, and he has gradually lost twenty-four pounds during the past ten months.

On admission Temperature 100.8, pulse 112, respirations 26, blood pressure systolic 110, diastolic 50

Physical examination now is practically the same as it was on

admission. The patient is quite alert and cooperative, although obviously acutely ill. He is orthopneic, and somewhat dyspneic, and he becomes very short of breath when he attempts to carry on a conversation or moves around in bed. The skin is warm and moist. Numerous small petechial hemorrhages are noted on close examination of the skin, and there are a few petechiae seen in the conjunctivae. There are no hemorrhages in the fundi, although several small exudates are noted. The tonsils are of moderate size and appear chronically infected. There is no enlargement of the thyroid. The lungs are clear. There is great enlargement of the heart, which measures 12 cm to the left in the sixth interspace and 5 cm to the right in the fourth interspace. The characteristic signs of mitral stenosis and incompetency as well as those of aortic incompetency are noted. One hears a rough systolic murmur at the apex transmitted well into the axilla, and a long apical diastolic murmur ending in a presystolic rumble and a loud first sound. The second pulmonic sound is accentuated. A loud low-pitched diastolic murmur is heard down the left border of the sternum. The radial pulse is quick and collapsing, and a capillary pulse is seen in the nail beds. The liver is greatly enlarged and tender, the edge being felt one hand's breadth below the costal margin. The spleen is palpable. There is no tenderness of the finger tips, no clubbing and no edema. Neurological examination is negative.

Laboratory Findings—

Blood—Red blood corpuscles 3,960,000, hemoglobin 13 Gm (90 per cent), white blood corpuscles 9,950

Urine—Albumin 1+, sugar 0. Microscopic—white blood cells ++, red blood cells +, casts +

Wassermann—negative

Nonprotein nitrogen—102 per cent

Liver Function Test—Bromsulphthalein—28 per cent retention after thirty minutes

Blood culture—1 colony of alpha streptococci per cc

Electrocardiogram—First degree heart block with P R interval 22. P waves small and notched. Q R S complexes thickened.

The clinical diagnosis is chronic rheumatic heart disease, mitral stenosis and incompetency, aortic incompetency, subacute bacterial endocarditis, cardiac insufficiency.

REMARKS BY DR. LOUIS HAMMAN

This patient is presented to you not as an example of some rare disease, nor yet to demonstrate unusual features of one better known, but merely because he illustrates so well the typical manifestations of a not uncommon disorder. Subacute bacterial endocarditis was first recognized as a distinct disease at the beginning of the century and since then has received particular attention at this hospital where Osler made his early studies. For many years only physicians practicing at large medical centers recognized the characteristic clinical features of the disease but more recently the wide spread use of laboratory methods of examination has made the condition a familiar one to the general practitioner. Therefore, it is needless to comment upon the well-developed, typical form of the disease. In the case before you the diagnosis was made at once by the interne after only a casual examination and without aid from the laboratory.

Subacute bacterial endocarditis is nearly always caused by the *Streptococcus viridans*, although at times the *Influenza bacillus* and the *Gonococcus* may be the infecting organism. It is a peculiarity of the *Streptococcus viridans* that it seldom attacks a healthy valve but as a rule settles upon a valve already injured by disease or congenitally deformed. This preceding disease usually is rheumatic fever, and *Streptococcus viridans* infection is a frequent cause of death when the heart has been crippled by rheumatism. Only rarely does this organism lodge and grow upon the aortic valves rendered incompetent by syphilis. Therefore, every heart which is the seat of a valvular defect or of a congenital deformity is liable at some time to have a *Streptococcus viridans* infection engrafted upon it. In diagnosis it is important to bear this fact in mind. If examination reveals the presence of a valvular lesion we must always consider the possibility that a bacterial infection of the valve has occurred and search carefully for evidence which may betray it.

I. Fever is the symptom which most often arouses suspicion. It need not be high for often there is not more than a daily rise of one degree and sometimes even of less. When fever is present it must be satisfactorily explained by some other cause before the possibility of bacterial endocarditis may be dismissed. The common causes of fever in heart disease are these: (a) When the heart fails there is almost

regularly a little fever caused by the accompanying changes in the circulation and not by infection. It is characteristic of this fever that it disappears when circulatory efficiency is re-established, to come on again should the heart fail once more. (b) Very frequently a mild infection, especially a respiratory infection, ushers in the symptoms of myocardial failure. The fever may then persist for days and under these circumstances it is difficult to decide how much of the fever is due to infection and how much to the circulatory failure. (c) Complications directly caused by the heart disease are often accompanied by fever. These are chiefly embolic accidents and especially often pulmonary embolism with infarction. (d) Specific infections which are the direct cause of valvular lesions are usually febrile diseases. The one we have particularly in mind is rheumatic fever. There is abundant evidence to justify the current view that rheumatism is a chronic infection and that when the infection is once acquired it may persist for many years, perhaps, in a latent form, throughout a lifetime. According to this view recurring rheumatic manifestations are recrudescences of an established infection and not successive fresh infections. It is characteristic of rheumatism that it is often accompanied by fever of long duration. Therefore, it may be extremely difficult when faced by the combination of fever and a valvular lesion to distinguish between subacute bacterial endocarditis and active rheumatic infection.

II Anemia, usually of moderate degree, is a characteristic symptom of subacute bacterial endocarditis. Unfortunately, from the standpoint of diagnosis, it is equally characteristic of the rheumatic state. When a patient with a valvular lesion has protracted fever and anemia we may be reasonably sure that the symptoms are due either to bacterial endocarditis or rheumatism, but from the clinical data it may be impossible to decide with assurance which of the two is at fault. The distinction is an important diagnostic problem and the postmortem discloses many surprises.

III The spleen is almost regularly enlarged in subacute bacterial endocarditis whereas it is seldom enlarged in rheumatic fever. This is an important point in differential diagnosis for, if in addition to a valvular lesion, fever and anemia, the patient has an enlarged spleen, it is probable to a high degree that the disease is bacterial endocarditis.

IV When in connection with these symptoms embolic phenomena

are observed then the diagnosis is assured. Embolic phenomena show themselves most often in the form of petechial spots in the skin, the mucous membranes and the retina. Therefore, these locations must always be inspected carefully and repeatedly when there is a suspicion of the presence of bacterial endocarditis. Next in diagnostic importance are emboli to the kidneys which betray themselves by the transient appearance of red blood cells in the urine. Therefore, the urine should be examined daily when the diagnosis is in question. It must be remembered that if the bacterial infection is located upon the valves of the right side of the heart no embolic phenomena occur in the general circulation. Emboli then go to the lungs and, if they are numerous, pulmonary symptoms may dominate the clinical manifestations and pulmonary tuberculosis be diagnosed. When we are confident that a patient has active subacute bacterial endocarditis and we search again and again but in vain for petechiae and transient hematuria, we may confidently assume that the lesion is situated within the right side of the heart.

V Clubbing of the fingers and erythematous nodes at the finger-tips are interesting manifestations of the disease and sometimes aid in diagnosis. Since, as I have said, the diagnostic problem usually is to distinguish between bacterial endocarditis and rheumatism it is important to point out that clubbing of the fingers occurs only rarely in connection with rheumatic heart disease. In bacterial endocarditis clubbing may come on with astonishing rapidity, within a few weeks, and when it develops under the eye of the observer it is a distinctive symptom.

VI Although the diagnosis of bacterial endocarditis can usually be made without the aid of blood cultures, still these never should be omitted because when positive they put the final stamp of certainty upon the diagnosis and tell us what particular organism is the infective agent. A single negative culture has no value in excluding the diagnosis and many repeated cultures may remain sterile even though an active infection be present. When cultures are persistently negative, although the characteristic symptoms of bacterial endocarditis are present, then we may surmise that the Gonococcus is the infecting organism.

We are interested particularly in instances of bacterial endocarditis which run a very mild and prolonged course. Often there are

long periods during which the temperature is normal or nearly so and never is there more than a little fever. We are interested in them because of the diagnostic difficulty, for the autopsy revelation often comes as a great surprise, and also because what we observe at autopsy convinces us that bacterial endocarditis must often heal. Only recently we saw demonstrated the postmortem findings upon a colored man fifty-one years of age who had been first observed in the Out-patient Department of this hospital in December 1933. At that time he had a well-developed aortic insufficiency. The Wassermann reaction on the blood serum was strongly positive and the roentgenogram demonstrated a dilated and tortuous aorta. The evidence warranted the diagnosis of syphilitic aortitis with aortic insufficiency which was confidently made. The patient returned to the hospital and entered the ward nearly three years later, in September, 1936. He said that after his previous visit he had been quite comfortable and got on well until about six weeks before when shortness of breath had again come on and had steadily increased. On this admission the patient had the characteristic symptoms of myocardial failure, though only to a moderate degree, and examination again disclosed the presence of aortic insufficiency and dilatation of the aorta. However, now the matter of greater importance was an abscess situated in the lower lobe of the right lung which was correctly thought to be due to an infected and necrotic infarct. The patient had high fever and became progressively more and more deeply intoxicated. He died of the pulmonary infection, not of heart failure, eighteen days after entering the hospital. At the postmortem the aortic valves were greatly thickened and deformed, in places calcified. The valves consisted of only two leaflets, due, there can be little doubt, to a congenital anomaly. Along the borders there were a few bacterial vegetations. There was not the slightest evidence of syphilis or of rheumatism. One could not suppress the thought that had the patient lived a little longer the bacterial endocarditis would have healed completely. The important point to emphasize is that here there were no symptoms to suggest bacterial endocarditis. It is only reasonable to assume that the infection was present and active at the time the patient was first examined three years before death.

Now and again we see at autopsy an old, thickened, deformed valve when none of the usual marks of a syphilitic or rheumatic in-

fection are present. Then we speculate upon the nature of the original valvular disease. The appearance of the valves is so extraordinarily like that of the valves of bacterial endocarditis which has *almost* healed, that we are encouraged to believe that they do in fact represent completely healed instances of the disease.

I cannot omit mentioning, even though I do so briefly, some of the complications which give this interesting infection a colorful and varied clinical course. These complications arise chiefly from emboli and mycotic aneurysms, but some of them and especially one, namely, diffuse glomerular nephritis, are the direct result of the infection. I have already said that numerous pulmonary emboli may lead to the diagnosis of pulmonary tuberculosis. Occasionally a pulmonary infarct may break down and form a pulmonary abscess. A young adult may have a sudden hemiplegia as the first severe symptom of the disease.

A short time ago a young white man entered the hospital complaining of intense abdominal pain. He had fever and moderate leukocytosis. There was great uncertainty about the diagnosis and the advisability of performing an exploratory laparotomy was seriously considered. It had not been overlooked that an aortic insufficiency was present but this seemed unrelated to the acute abdominal crisis. It was only when the routine blood culture was reported to show *Streptococcus viridans* septicemia that any connection between the two was suspected. At the autopsy, performed a few weeks later, it was demonstrated that the abdominal symptoms had been due to a mycotic aneurysm of a mesenteric artery. In another instance of the disease sudden death was due to the rupture of a mycotic aneurysm at the base of the aorta with hemorrhage into the pericardial sac. It had been suspected clinically that the sudden death was due to coronary occlusion for not infrequently, when vegetations grow upon the aortic valves, strands of vegetation wave in the aortic blood-stream until some favoring current carries them into a coronary orifice.

In bacterial endocarditis two kinds of renal lesions occur, the focal lesions which follow emboli and diffuse glomerular nephritis similar to the nephritis of hemolytic streptococcal infections. The embolic lesions give useful diagnostic symptoms but never seriously impair renal function, the diffuse glomerular nephritis may cause great impairment of renal function and rapidly lead to death from

uremia. Occasionally under these circumstances the true nature of the underlying disease may be overlooked. I recall a colored man who entered the hospital many years ago with the symptoms of advanced nephritis and he died of uremia a few weeks later. There was also a typical aortic insufficiency. What other symptoms may have been present I do not recall, but I thought at the time and still think the suggestion of the then Resident Physician, Dr. Arthur Bloomfield, that the patient had bacterial endocarditis was a very brilliant one and autopsy demonstrated the suggestion to be correct.

7 Sickle Cell Anemia with Cardiac Complications

By JOHN T KING, JR, M D
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and

CHARLES A JANEWAY, M D
Assistant Resident Physician

CASE presented by Dr Charles A Janeway

This seventeen year old colored school girl first became known to the hospital at the age of nine, when she was admitted to the Harriet Lane Home because of a cold and pain in the side. For several years before she had had anorexia, vomiting after meals, and severe frontal headaches. Her acute illness had begun three weeks before admission, with nasal discharge, sore throat, and fever, followed by generalized aches and pains, with acute pain in the right lower chest, aggravated by breathing or rubbing her side. The nasal discharge became purulent, and because of cough, dyspnea, and severe nosebleeds she was admitted on January 4, 1928 with a temperature of 100°, pulse of 96, and respirations of 36. Important physical findings at that time were large, pale tonsils, fine rales at the lung bases, enlarged liver, and definite cardiac abnormalities. The heart was enlarged to right and left, with bulging and a marked lift of the precordium with each systole. Sounds at the apex were loud and sharp, with a high pitched systolic murmur and a high pitched blowing diastolic murmur, while at the base the first sound was fainter, second sound split, $P_2 > A_2$, with a high pitched systolic murmur, and a short diastolic whiff in the pulmonic area. Blood pressure was systolic 100, diastolic 50.

Laboratory Examinations —

Urine Essentially negative, but a faint trace of albumin present

Blood Moderate anemia with hemoglobin 60 per cent, red blood corpuscles 2,880,000, white blood corpuscles 14,500

Roentgenograms "Heart at upper limits of normal size, consolidation at right lung base, and marked root infiltration, suggestive of

tuberculosis" Later chest plates showed clearing in the lungs, but persistent slight cardiac enlargement

Electrocardiogram Rate 107, sinoauricular tachycardia, P-R interval 18 second (prolonged for patient's age), T₁ and T₂ upright, T₃ inverted

Course in the Hospital—Patient remained on the ward for five months Because of the fever, elevated white count (14,000 to 25,000), persistent cardiac enlargement with murmurs in systole and diastole, prolonged P-R interval, and frequent nosebleeds it was assumed that the patient had acute rheumatic fever, and she was given salicylates without any improvement Subsequent examinations revealed marked autoagglutination and sickling of the red blood cells and an increased excretion of urobilin in stool and urine, which decreased following transfusion She was given small transfusions, her tonsils and adenoids were removed, pus was irrigated from her antra, and finally twenty-three weeks after admission she was discharged—subjectively much improved with hemoglobin of 51 per cent, red blood cells of 2,550,000

For the next three years the patient was followed in the Cardiac Clinic of the Harriet Lane Home, where a persistence of her cardiac enlargement, systolic murmur, and low hemoglobin were noted The diastolic murmur gradually disappeared over the course of a year and a half She had frequent nosebleeds and severe headaches, and despite small intramuscular injections of blood her hemoglobin fell slowly until it reached 20 per cent with red blood cells of 640,000 and she was admitted for a second time in May, 1931 Findings were essentially the same, with electrocardiogram showing a P-R interval from 20 to 24 seconds on the same record After six weeks she was discharged greatly improved

Since then she has had fair health, with some fatigue, occasional headaches, and epistaxes, two of which were severe enough to necessitate admission in 1934 On these two admissions her condition was as before—fever, moderate anemia, elevated icterus index, cardiac enlargement, systolic murmurs, prolonged conduction time At times she had had mild aching pains in the extremities, and in 1932 she struck her right shin, and it became too painful for walking for ten weeks This pain recurred three months later, and a roentgenogram of the tibia showed nothing at that time

For the two and a half years since her last admission the patient has been leading a fairly normal life, attending school, with her only difficulties mild pains in her legs, headaches and nosebleeds. Her present attack began with a head cold, followed in three weeks by mild aching in the shoulders and neck. The next day she developed a severe drawing pain in the left ankle which gradually grew worse until there was terrific pain extending from the left foot to the hip and even up to the left lower quadrant of the abdomen. Pain finally became so severe that she entered the hospital three days after its onset.

Physical Examination (November 9, 1936) — Temperature 100°, pulse 100, respiration 20, blood pressure systolic 132, diastolic 70.

A well developed and nourished colored girl of seventeen, evidently in severe pain, protecting her left leg. Skin and mucous membranes normal. Sclerae showed slight greenish discoloration. Nose, throat, and teeth innocent, with a few small palpable glands at jaw angles. Chest clear. Heart somewhat enlarged to percussion, left border of dullness 9 cm in fifth space, right border 4 cm fourth space, with no increase over aorta or conus area. At apex, first sound largely replaced by loud, rasping systolic murmur, second sound followed by a low pitched rumbling sound in mid-diastole, taken by some observers to be a definite murmur, by others as a third heart sound. Pulmonic second sound louder than aortic. Peripheral vessels soft with quick, bounding pulse. In the abdomen, liver felt just below costal margin, spleen felt by some observers. Acute tenderness of the left leg from knee to ankle, with skin hot, shiny, and a little tense, with bluish discoloration along the instep. Right tibia roughened, but not tender.

Laboratory Examinations —

Urine Negative, except for strongly positive urobilin test.

Blood Hemoglobin 62 per cent, red blood corpuscles 3,400,000, white blood corpuscles 14,500, differential polymorphonuclears 61 per cent, Juvenile polymorphonuclears 4 per cent, myelocytes 2 per cent, lymphocytes 21 per cent, monocytes 8 per cent, basophiles 3 per cent, eosinophiles 1 per cent.

Stained Smear showed slight achromia, marked poikilocytosis and microcytosis of red blood corpuscles, moderate number of sickle cells, and abundant platelets — 17 per cent reticulocytes.

Fresh preparation showed marked autoagglutination of the red

cells, with moderate sickling at first, becoming very marked after twenty-four hours

Icterus Index 20, *Van den Bergh* indirect reaction, 33 mg per cent

Sedimentation Rate 10 mm /hour (uncorrected)

Flocculation Test for Syphilis—negative

Roentgenograms of Chest showed increased transverse diameter of heart, aorta normal, lungs clear, *of Bones* negative except for skull which showed thickening of calvarium and perpendicular striations in outer table of parietal bone, and right tibia with an area of destruction in lower part of medullary cavity without cortical thickening or periosteal reaction Left tibia negative

Electrocardiogram Sinus rhythm, rate 83, P-R interval 22 seconds, T waves upright First degree heart block

An investigation of the family showed the sickle cell trait present in father, mother, and four of the six siblings examined Two of these had mild anemia, and of these one has been followed since the age of six as a case of probable rheumatic fever and rheumatic heart disease

To sum up, therefore, we present a case of obvious sickle cell anemia in a seventeen year old colored girl, who is a diagnostic problem, because in addition to pains in the extremities, frequent upper respiratory infections, and cardiac enlargement with systolic murmurs, she had had a definite diastolic murmur at times, and a prolonged P-R interval, varying from 18 to 24 seconds during the eight years in which she has been followed

REMARKS BY DR. JOHN T. KING

This case is distinctly within the province of the Southern Medical Association, for although the sickling trait affects the red blood count of a small proportion of white people, sickle cell anemia is to all intents and purposes a disease of the negro A few of the findings in this case deserve some comment In the first place, the blood findings are quite characteristic, as are also evidences of increased hemolysis, as indicated by the blood and urinary findings, as well as the moderate icteric discoloration of the sclerae An exception to the complete picture of sickle cell anemia in this case lies in the absence of leg ulcers The skin is quite intact, however, there are definite

roentgen ray changes in the medullary portion of the lower right tibia. On the left side, although the roentgenograms of the bones show no abnormality, there is exquisite superficial tenderness and increased heat over the lower third of the leg, particularly in front. It is not altogether clear what causes leg ulcers in these cases, and it does not seem to put too much tax on the imagination to think that the present state of inflammation of the ankle, a site commonly involved with ulcers, may represent an early stage in the development of leg ulcers.

Then, the spleen in these cases is interesting. The pathology has been well described at a recent meeting of this Association. Hemorrhage, fibrosis and eventual atrophy of the spleen seem to be characteristic. The spleen in our patient is readily felt, small and hard. Although most spleens when palpable are enlarged, this spleen actually feels smaller than average, but is somewhat further forward than is usually the case.

The chief interest in this case, however, lies in the cardiac condition. The patient presents a typical picture of mitral insufficiency. Were it not for the presence of sickle cell anemia, the conclusion would be obvious that the patient has rheumatic heart disease with mitral insufficiency. I am inclined to consider the findings in diastole an exaggerated third heart sound rather than an indication of mitral stenosis. Further, there is no increase in the size of the pulmonary conus as reflected in the roentgenogram, nor is there any reduction in the size of the pulse. The difficulty in sickle cell anemia lies in the fact that cardiac hypertrophy, apical systolic murmurs, and prolongation of the auriculoventricular conduction time all seem to occur as a part of this disease syndrome. There are a number of reports in the literature in which the diagnosis of rheumatic heart disease with mitral insufficiency was made during life and in which no endocarditis was found at autopsy. A case of this sort occurred at this hospital in recent years. Furthermore, Dr. R. C. Tilghman, the Resident Physician, suspecting that this patient might not have rheumatic heart disease, has inquired about the cardiac findings in sickle cell anemia treated at the Harriet Lane Home for Children at this hospital. He found other instances of prolongation of the auriculoventricular conduction interval in patients with sickle cell anemia and that in a high percentage of cases these children had en-

larged hearts of globular shape, with loud systolic murmurs. Since a prolongation of this interval is usually considered suggestive evidence of rheumatic heart disease in children, this finding is very important as it seems that every peculiarity of the heart in our patient can be explained by the presence of sickle cell anemia without the assumption that she has rheumatic heart disease as well.

8 Pulmonary Emphysema Complicated by Hyperthyroidism

By HENRY M THOMAS, JR, M D

Assistant Visiting Physician

and

THOMAS MCP BROWN

Assistant Resident Physician

CASE presented by Dr Thomas MCP Brown

The patient, a fifty-one year old Polish tin worker, admitted for the second time to the medical service of the Johns Hopkins Hospital, complained of cough and shortness of breath

Family history unimportant. Past health excellent except for gonorrhea in 1913. In 1932, he developed a cough which has been chronic ever since. The cough has been productive of small amounts of yellowish tenacious sputum. In 1932, his symptoms became so annoying that he sought relief in the Out-Patient Department, and chronic bronchitis and pansinusitis were found. He was not seen again until 1934, complaining then for the first time of shortness of breath on exertion and occasional swelling of his ankles. He was found to have emphysema, asthmatic bronchitis, a mild degree of myocardial insufficiency as well as chronic sinus infection. Two months later an ethmoidectomy was performed, the nasal polypi were removed, with, however, no subsequent relief from the steadily progressing symptoms. In September, 1934, he was noted to have a mild degree of hyperthyroidism with slight diffuse enlargement of the thyroid gland, exophthalmos and symptoms of sweating, nervousness and a history of a loss of thirty-six pounds in weight. He was admitted to the hospital for thyroidectomy. The highest basal metabolic rate was plus 34, and the lowest, minus one after iodine therapy and just prior to operation. The patient developed post-operative tetany the symptoms of which never returned after two months of calcium therapy. There was no diminution in the degree of shortness of breath following the thyroid operation. For the next two years, he was able to do part time work without symptoms sufficient to bring him to the hospital during this interval.

Five weeks before admission he developed a chest cold with severe exacerbation of the chronic cough and shortness of breath. Finally on November 16, 1936, he was brought to the Emergency Ward of the hospital in acute respiratory distress. The important points in the physical examination at this time were the labored respirations, the intense cyanosis, moist rales heard throughout both lungs and a moderate degree of pitting edema of the lower extremities. The diagnosis of acute pulmonary edema was made and a venesection was done immediately with the removal of 500 cc of blood. After thirty-six hours in an oxygen tent and with digitalis therapy the patient improved remarkably.

Physical examination now reveals a middle aged white man who no longer appears acutely ill. He coughs at frequent intervals and produces small amounts of mucopurulent sputum. The edema of the lower extremities has now disappeared. There is still moderate cyanosis of the face, lips, tongue and nail beds. Arteriosclerotic changes are seen in the vessels of the fundi, and the radial arteries are somewhat thickened. The neck veins are distended. There are present all of the characteristic signs of marked pulmonary emphysema. The chest moves very little with each respiration, the breathing being largely abdominal in type. The anterior-posterior diameter of the chest is deep and the costal angle is wide. The ribs anteriorly have a transverse appearance. Hoover's sign, although not marked, is present. There is no absolute cardiac dullness. The percussion note over the lungs is hyperresonant. The lung bases are low, and they do not move appreciably with the respirations. The breath sounds are very distant. Occasional sibilant rales are heard. The heart borders cannot be percussed with accuracy due to the emphysematous type of chest. The heart sounds are regular and distant, and no murmurs or accentuations are heard. Blood pressure systolic 122, diastolic 80. The liver margin is palpable three finger-breadths below the costal margin in the mid-clavicular line and it is quite tender on pressure. The remainder of the examination is essentially negative.

Laboratory Findings—

Blood Red blood corpuscles 5.9 million, Hemoglobin 16 Gm., White blood cells 9,500, Wassermann negative

CO₂ combining power—90 vols per cent

Serum chlorides 844 m eq /litre

Arterial O₂ content—14.7 vols per cent Arterial oxygen capacity 18.8 vols per cent O₂ saturation of arterial blood 80 per cent Venous O₂ content—9.6 vols per cent

Urine Negative

Teleoroentgenogram Enlargement of pulmonary conus, heart not otherwise enlarged, lungs essentially clear

Electrocardiogram Low voltage Thickening of Q R S complexes

Diagnosis Emphysema of lung, asthmatic bronchitis, chronic, cardiac insufficiency secondary to emphysema, hyperthyroidism relieved by operation

REMARKS BY DR HENRY M THOMAS, JR

We have heard the history of a man who has developed an advanced degree of obstructive emphysema after chronic bronchitis with cough and mucopurulent sputum for ten years. He presents, as we have been told, the classical features of emphysema with extreme cyanosis of the lips and fingers, the barrel-shaped chest with the hyperresonant percussion note, and with retraction of the costal margins during inspiration. This has been called Hoover's sign and is thought to indicate a permanently lowered diaphragm which, during contraction, cannot descend and therefore exerts all of its force in pulling the chest wall in. I believe that other mechanical forces combine to produce the retraction of the costal margins. Since we know that the chest of an emphysematous patient is held more or less permanently in a position of forced inspiration the further effort to expand the chest results in lifting it as a whole and causing a relative or absolute drawing in of the lower borders of the thorax.

The roentgenogram of the chest also is very characteristic of emphysema. The horizontal direction of the ribs, the wide intercostal spaces, the great increase of the transverse diameter of the chest all reveal marked emphysema. It is interesting that the heart is not enlarged although there is some increase of the pulmonary conus. The question of cardiac enlargement secondary to pulmonary emphysema is still a much disputed one. Evidence has been presented which seems to show that the heart is not increased in size to any

great degree and that when true heart failure occurs secondary to emphysema it is a terminal and final event

Clinically, it is frequently extremely difficult to differentiate between cardiac insufficiency and pulmonary insufficiency. Recently I became interested in an effort to establish a clinical test which would reveal the degree of pulmonary insufficiency. In the course of subjecting a patient suspected of having angina pectoris to the rebreathing test devised by Baker, I was struck by the amount of dyspnea and cyanosis produced in the patient at the end of two minutes, whereas an average individual can continue the test for five to seven minutes with little or no discomfort. The test consists of partially filling a Benedict-Roth metabolism apparatus with room air, leaving the soda lime in the apparatus as usual (Dr B M Baker advocates removal of the soda lime container to avoid the possibility of sudden collapse), and allowing the patient to breathe into the closed system, thereby gradually removing the oxygen and providing a steadily lessening oxygen mixture, thus producing an increasing anoxemia. Patients with angina pectoris usually experience cardiac pain in the course of four to six minutes, but rarely complain of dyspnea. The patient was a man of forty years whose complaint was substernal distress and dyspnea on exertion. There were no signs of cardiac failure except dyspnea on exertion and he had the classical physical findings of pulmonary emphysema. After the patient had returned to Florida it was borne in on me that this test might be used as a gauge of functional respiratory reserve. Since that time I have tested by this method eighteen other cases that presented various degrees of clinical emphysema, but in no other case has there been any evidence of increased susceptibility to reduced oxygen tension. I am at a loss to explain its occurrence in the first individual. It seems possible that the increased residual air which is present in cases of emphysema contains more total oxygen than exists in normal residual air and thus allows the rebreathing test to continue for an abnormally long time before producing noticeable dyspnea or cyanosis. In any event breathing air in which the percentage of oxygen is constantly being reduced does not offer a means of diagnosing and measuring functional impairment of the lungs in emphysema.

In emphysema the total lung volume, as estimated by Christie's

oxygen dilution method, remains essentially unchanged, but residual air is increased at the expense of complementary air and vital capacity is reduced McCann finds that when residual air is over 40 per cent of total capacity some degree of anoxemia exists and anoxemia increases more or less proportionally to the increase in the residual air It has been assumed that an increase in residual air and decrease in vital capacity cause inefficient alveolar ventilation, which in turn leads to diminished oxygen saturation of the arterial blood Either of these estimations (i.e., residual air or oxygen unsaturation of arterial blood) is closely correlated with dyspnea and is thought to afford a fair index of pulmonary efficiency It seems clear, however, that neither one expresses an accurate measure of potential pulmonary efficiency for any given individual

In our patient the oxygen unsaturation of the arterial blood is 20 per cent which is high indeed and which explains the extreme degree of cyanosis In conjunction with this the CO₂ combining power is extraordinarily high and is an indication of the resistance that patients with emphysema develop to high saturation of CO₂ In this patient the amazingly high figure of 90 vols per cent CO₂ combining power was present It has long been known that such patients can breathe a high concentration of CO₂ without subjective or objective discomfort although when the percentage is raised too high, they suddenly go into collapse In this connection it is interesting to compare the functional compensatory changes which take place in individuals who live in a high altitude Talbott and Dill report in the November number of the American Journal of Medical Sciences observations made on patients suffering from mountain sickness who live at an altitude of 17,500 feet above sea level in Chile Such patients are cyanotic, have an increase in the number of red blood cells, are dyspneic on exertion, have an emphysematous-like contour of the chest but with an increased vital capacity The significance of this is quite clear The emphysematous-like contour of the chest is brought about in the course of compensatory increase in the oxygenating power of the lung An increased residual air is associated with an increased vital capacity and this permits the lung to provide for the blood stream a greater quantity of air which contains a smaller percentage of oxygen than normal In the emphysematous patient the lung becomes less and less efficient and its functional reserve is

constantly called on to maintain an increased residual air. This, in turn, encroaches on the vital capacity so that the disproportion between residual air and vital capacity finally gives rise to chronic respiratory decompensation.

The oxygen unsaturation that is seen in our patient (20 vols per cent) is also seen in patients living at high altitudes and therefore may be considered a secondary compensatory mechanism as is the increase in the number of red blood corpuscles. The oxygen unsaturation which occurs in emphysema has led many observers to wonder whether when the patient is exposed to pure oxygen in the basal metabolism test the initial withdrawal of oxygen from the machine may not be used to restore the oxygen unsaturation to normal. My observations on this patient and others with emphysema show that there is no difference in the rate of withdrawal of oxygen from the metabolism apparatus when room air or pure oxygen is used. These observations lead me to believe that the ordinary basal metabolism test is reliable in patients with emphysema.

It is extremely interesting to speculate on the occurrence of hyperthyroidism in this patient. Dr. Cowles Andrus in this clinic thought it possible that prolonged oxygen want might lead in many cases to a low grade hyperthyroidism. If this were true, he thought, a most plausible reason for the time-honored use of potassium iodide in the treatment of emphysema would be at hand. This patient was noted to obtain marked symptomatic relief after taking potassium iodide, and his metabolic rate fell from plus 34 to minus 1 under this form of treatment. Dr. Andrus has observed a number of other cases without finding any in which there was an elevation of the basal metabolic rate. We must believe, I think, that the development of hyperthyroidism in this case was an accidental occurrence, although hyperthyroidism is not uncommon in people living in high altitudes.

The first lantern slide shows rebreathing test on this patient. The first curve represents the amount of oxygen withdrawn from room air and the second curve the amount withdrawn from pure oxygen, approximately an equal amount.

The second slide is from another patient with moderate emphysema. The curve represents reduction in vital capacity and inability to exhale reserve air following deep inspiration. This is a characteristic curve which was first noticed by Christie in patients with

emphysema McCann confirmed this finding in some cases but not in others. The inability to expire normally after a deep inspiration was thought by Christie and others to be brought about by the loss of pulmonary elasticity. However, it seems to me that there is no reason to believe that the lung would shrink further from a partially distended state than it would from a fully distended one. Expiration is a passive movement during quiet breathing and becomes active only during dyspneic breathing. In a normal person, with normal chest wall-lung breathing mechanism, need for greater respiratory activity is supplied by more rapid ventilation of a normal or temporarily slightly increased residual air. This is done by larger inspiratory movement followed by an associated active expiratory movement with the result that the proportion of tidal air to residual air is increased. In other words, the life long habit of response to a need for more rapid ventilation of the lungs is an increased inspiratory effort with only a secondarily increased expiratory effort. When, for whatever reason, residual air is permanently increased as it is in emphysema, tidal air is constantly increased to maintain the required residual air/tidal air proportion. This increase in tidal air on top, as it were, of an increased residual air encroaches on complementary air and brings about breathing at a higher and less efficient resting point. The larger residual air could be more rapidly ventilated when need be if tidal air could be increased partially at the expense of residual air but the life long unconscious training of forced breathing is in the direction of voluntarily increasing inspiration and allowing expiration automatically to keep pace. In patients with emphysema, the act of forced expiration is unable to keep pace with forced inspiration. Reserve air can be expired only when forced expiration starts from the top of tidal air, that is, from the end of a normal unforced inspiration. For this reason in our clinic we are training emphysematous patients to start the respiratory cycle with forced expiration and to allow inspiration to take care of itself. It is too early to report the results of this practice but temporarily improved breathing has been noted.

Kerr has devised a belt to be worn by the obese emphysematous patient and the slide which you are now looking at is from his article in the November number of the *Annals of Internal Medicine*. One important feature of this belt is the elastic lateral sections which are

made of two pieces of firm elastic goring six inches wide and approximately seven inches long placed one above the other. The effect of the partially elastic belt is to provide what might be spoken of as artificial abdominal respiration which as Kerr says "aids, rather than suppresses abdominal breathing, and prevents limiting respiration to the thorax, as is seen in obese states naturally or where a firm, inelastic belt is applied. The increased elasticity also aids in expiration, and overcomes the prolonged expiratory period seen in those patients with depressed diaphragms due to abdominal ptosis or emphysema. The diaphragm more readily assumes the expiratory position and is ready to descend with the next inspiration. There is no decrease in the supportive effect during the inspiratory expansion." Most cases of emphysema are greatly aided by a firmly fitted abdominal support and one of the Kerr variety is to be chosen when available.

We have presented a patient with extreme pulmonary emphysema following chronic bronchitis who has suffered from hyperthyroidism which was relieved at operation and thereby allowed the patient to continue work until the disability from emphysema became too great. I have indicated theoretical and practical aspects of therapy in this condition.

9 The Diagnosis of Acute Arthritis

By CHARLES W WAINWRIGHT, M D
Assistant Visiting Physician

and

CHARLES A JANEWAY, M D
Assistant Resident Physician

CASE presented by Dr Charles A. Janeway

This thirty-six year old colored housewife entered the hospital on November 13, 1936, because of fever, joint pains, headache and delirium

Family History Non-contributory

Past History No sore throats, but frequent head colds Three teeth removed in the past No serious illnesses All her troubles related to pregnancy, a state which she enjoyed twelve times, with twelve spontaneous deliveries at term and ten living children During the last few pregnancies, she had vomiting in the early months and exertional dyspnea and ankle edema in the latter months Nocturia twice all her life, but this had increased to three or four times in the past few years She had complained at various times in the past few years of chills, fever, burning and frequency, but only on one occasion did examination confirm the clinical impression of pyelitis This was in 1932, when her blood pressure was noted to be systolic 184, diastolic 110 Since then her blood pressure has fluctuated from a low of systolic 110, diastolic 80 to a high of systolic 220, diastolic 140 Highest readings were usually found within a week or two after delivery, with fairly normal pressure during pregnancy There was a history of one episode of bloody diarrhea lasting a week ten years ago

Present Illness As a child the patient had growing pains in the arms and legs, especially during cold damp weather At the ages of twenty-seven and thirty she had recurrences of this rheumatism with aching pains in one shoulder and knees but no swelling and without severe enough constitutional symptoms to send her to bed Fifteen months ago, at the age of thirty-five, in August, 1935, she was

admitted to this clinic because of joint pains and fever. She had had migratory pains in the right foot, ankle and wrist for five days, without any previous infection except possibly a finger which was somewhat sore following a laceration by a tin can. On admission she had fever of 103.6°, tachycardia of 140, a white count of 13,720 with a rapid sedimentation rate (36 mm in an hour, corrected). The right wrist, knee and ankle were hot, swollen and tender, while the heart was enlarged to the left with a loud systolic murmur heard all over the precordium. Blood pressure was systolic 182, diastolic 118. The urine examination was negative. She remained in the hospital for six weeks, with a gradual fall of temperature and subsidence of her joint condition during the first five days on moderate doses of aspirin (at first 2.4 gr, later 3.6 gr per day). There were no further symptoms of fever for the rest of her stay, except at one point in the second week when aspirin was omitted. She was afebrile the last two weeks without aspirin. Roentgenograms of her joints showed nothing but periarticular swelling. There was no change in the heart murmurs during her stay. A gonococcus complement fixation reaction was negative, and cervical smears failed to show any gonococci. She was therefore considered as a case of infectious arthritis complicated by hypertensive cardiovascular disease.

Following discharge she got along in her usual way, being troubled with mild headaches, vertigo, and slight dyspnea on strenuous exertion. Despite the dire warnings of the doctors she became pregnant for a twelfth and last time, was delivered after an uneventful period of gestation on October 1, 1936, just six weeks before admission. Her blood pressure rose nine days after delivery to systolic 220, diastolic 120 after being systolic 160, diastolic 110 shortly before delivery, but she went home in apparently good health.

One week before admission she began to have severe pain in the lumbar spine. This lasted two or three days and then jumped to the left shoulder, then to the wrists, ankles, fingers and toes with swelling of the feet and backs of the hands. Four days before admission she developed fever, and alternate chilly and hot sensations. Finally, on the day of admission after a domestic upset she developed a throbbing violent headache. That night she woke in a delirium, jumped out of bed screaming and was brought here and admitted on November 13,

1936 Patient denied any preceding infection except a cold six weeks before at the time of delivery

Physical Examination On admission Temperature 102 4°, pulse 132, Respirations 34, Blood pressure, systolic 150, diastolic 100 A large obese colored woman protecting her left arm, not appearing acutely ill Skin warm and moist, sweating profusely Marked tenderness about left shoulder, slight tenderness of left ankle and elbow Backs of hands puffy, but no other joint swelling Voluntary limitation of motion of wrists and left shoulder because of pain Fundi—arteries narrowed and tortuous with moderate compression of veins by arteries Neck veins not engorged, no dyspnea or cyanosis Tonsils large and ragged, but not particularly red Condition of teeth fairly good Lungs clear Heart moderately enlarged to left, with moderately loud sounds of good quality, a loud rather rough systolic murmur heard most prominently at pulmonic area At base pulmonic second sound a little louder than aortic, but both accentuated No diastolic murmur heard Peripheral arteries moderately thickened with bounding, rapid, regular pulse Abdomen normal except for liver edge 1 to 2 cm below costal margin No edema of extremities Reflexes not tested

Laboratory Examinations —

Urine Specific gravity 1023, acid, amber, albumin 3+ no sugar, 2 to 5 red blood cells, 3 to 5 white cells and many coarse granular casts in a catheterized specimen

Blood Hemoglobin 70 per cent, Red blood cells 4 15 million, White blood cells 23,100 with 73 per cent polymorphonuclear leukocytes Wassermann reaction negative Blood culture sterile

Electrocardiogram Normal sinus rhythm, rate 107, P-R Interval 18 seconds, slight thickening of QRS complexes, T waves upright Only abnormal finding, an upright T wave in chest lead

Roentgenogram of Chest Transverse diameter of heart enlarged, especially to the left and aorta slightly dilated Configuration of left border does not suggest the usual picture of mitral stenosis There are some vascular changes in the lung

Blood Chemistry Nonprotein-nitrogen 36, Uric Acid 2 6 milligrams per cent (blood plasma)

Course in the Hospital — Because of her acute arthritis with its discomfort the patient was started on aspirin 3 6 gr per day On this

dose her temperature fell slowly, headache disappeared, and on the fourth day after admission the patient seemed much improved with temperature only 100° and joints less painful. However, that afternoon her temperature rose to 102° and then climbed irregularly but steadily upwards until it reached 105.4° on the tenth day after admission despite 4-8 gm of aspirin a day. The patient became very ill, complained bitterly of severe headache and pain in the back of her neck, became delirious and very difficult to manage. Swelling and tenderness of the joints increased and the left knee became quite swollen and tender. This was tapped, 35 cc of thick, greenish, cloudy fluid being obtained. The cell count was 15,000/mm with 90 per cent polymorphonuclear cells and 10 per cent mononuclears. Blood cultures taken during this period failed to show any growth, either under aerobic conditions or under a high CO_2 tension.

REMARKS BY DR. CHARLES W. WAINWRIGHT

We frequently see, in the Wards of the Johns Hopkins Hospital, cases of acute polyarthritis which present such varied features that accurate diagnosis is often much delayed and at times never made with certainty. Often long continued observation decides the question when our more precise methods for diagnosis have failed. This situation is probably most frequently seen on the colored wards for the reasons that gonococcal infection is so prevalent in this race and because the climate of Baltimore permits us at times to see the more severe articular manifestations of acute rheumatic fever, so common in less temperate climates. Furthermore, we see the acute type of non-suppurative arthritis familiar to us all as a sequel of scarlet fever and tonsillitis, and at times, following less definitely streptococcal upper respiratory infections. It is then for the purpose of discussing the problems in the diagnosis of acute arthritis that this case is shown.

The patient is suffering from an acute polyarthritis which has been to some degree, at least, migratory and now involves the wrists and left shoulder. These joints are acutely tender, swollen and somewhat reddened and motion is extremely painful. There is rather marked constitutional reaction, with fever and leukocytosis. The condition at once suggests a gonococcal arthritis or rheumatic fever but in the differential diagnosis acute rheumatoid arthritis must be considered. This type of acute joint reaction is all too commonly

thought to be acute rheumatic fever, but must be set apart, as the serious complications of rheumatic fever do not occur in this type of acute arthritis. Other less frequently occurring joint conditions are not suggested and it is the differentiation of the three above diseases which is usually the problem in diagnosis in acute arthritis.

Acute Rheumatoid Arthritis — The term is restricted to that type of acute joint inflammation with fairly rapid onset, which is frequently preceded by an acute upper respiratory infection, often streptococcal, but occasionally less definitely so. At times no history of previous infection is obtained. In this type of acute arthritis the constitutional symptoms are often pronounced and the relation to infection preceding its onset by from two to four weeks closely simulates that seen in rheumatic fever. It is usually not so migratory as rheumatic fever and joint involvement is much longer maintained. There is much less, if any, favorable response to salicylates, but in most instances the joint reaction subsides completely and the cardiac complications of rheumatic fever do not occur. It is commonly seen at a later age period than the initial attack of rheumatic fever and this woman is now in the fourth decade. It may make its appearance more than once after having previously completely subsided and this patient had such an experience fifteen months before, which was considered an acute "infectious arthritis." The rapid onset, acute joint manifestations, pronounced constitutional reaction comparatively short course and usually its complete subsidence rather than its passing over into a chronic arthritis set it apart from chronic rheumatoid arthritis. And too, the infrequency with which small joints are involved and the lack of symmetrical joint involvement are unlike the latter. Although the entire course is acute the rapid joint destruction of gonococcal arthritis does not occur and after subsidence the joint is, in most instances, at least functionally normal. Of course in any of the types of joint disease under consideration the sedimentation rate of the red blood cells is elevated and is of no value in their differentiation. However, in acute rheumatoid arthritis the antihemolysin titre of the serum is frequently elevated as in rheumatic fever, especially when the history of preceding infection, likely streptococcal, is obtained. On the other hand, the agglutination of hemolytic streptococci as shown so regularly by the chronic form of rheumatoid arthritis of at least six months standing is not obtained. The duration

of the joint reaction here and its apparent lack of response, at least, in its earlier stages to salicylates is more suggestive of an acute rheumatoid arthritis than rheumatic fever. Subcutaneous fibroid nodules, seen in the chronic form of rheumatoid arthritis and in acute rheumatic fever are not seen in acute rheumatoid arthritis. And the various types of erythema, at times seen in rheumatic fever, are not seen here. This patient has had one isolated attack of acute polyarthritis with apparent complete subsidence but the history would indicate some degree of joint reaction as early as eleven years of age and ill defined evidences of its periodic reappearance from that time on. This feature is distinctly unlike the acute form of rheumatoid arthritis and the patient's subsequent course make such a diagnosis unlikely.

Gonococcal Arthritis—The frequency of gonococcal infection in this race makes the exclusion of gonococcal arthritis necessary when such an acute arthritis presents itself. The history of the recent occurrence of the primary gonococcal infection is never so striking in the female as in the male and the frequency of chronic pelvic infection makes the time relationship to the initial infection of less importance in the female. Even in the male acute gonococcal arthritis may occur many months after the acute urethritis and its close association with the primary genital infection is less common than previously thought. Nor is the occurrence of a monoarthritis in gonococcal infection so regular as formerly supposed and often a polyarthritis is present though there is a tendency in this disease to settle into one or two more stubborn joints. The fever, the leukocytosis, and the acuteness of the joint manifestations suggest a gonococcal infection. The joint fluid is usually more purulent than seen here, but the greenish color of the fluid obtained from the knee joint is considered quite characteristic of a gonococcal joint and the degree of cellular response in the joint fluid, with such a large percentage of polymorphonuclear neutrophiles is suggestive of gonococcal infection but is not incompatible with rheumatic fever. Neither tendon sheath involvement, so common in gonococcal arthritis, is present here, nor are any of the eye complications which are so frequently seen. In acute gonococcal arthritis we are dealing with a metastatic joint and the isolation of the organism would prove conclusively the nature of the arthritis. Unfortunately, the recovery of the gonococcus is difficult and so frequently

this conclusive evidence is lacking. However, the gonococcal complement-fixation reaction is proving itself more and more dependable and is found positive in such a large percentage of cases as to be almost as useful in diagnosis as is the Wassermann reaction, in the diagnosis of syphilis. The negative test here a year before this admission is strong evidence against a gonococcal arthritis and subsequent tests during this admission were likewise negative. However, this test must be interpreted with caution. At times the ability to fix complement may remain in one's serum for months or even a few years following a gonococcal infection. Under such circumstances a totally unrelated acute arthritis may develop, and by absolute reliance upon the complement fixation reaction one may be readily led astray. In addition, no gonococci could be found in the cervical smear in this case. Too, the number of pregnancies this patient has had militate against any serious degree of pelvic inflammatory disease. Roentgen ray evidence is of little value in establishing the diagnosis of gonococcal arthritis but at times the rate of joint destruction as demonstrated by roentgen ray is so rapid as to strongly suggest a gonococcal joint. The leukocytic response in gonococcal arthritis as well as in rheumatic fever is usually pronounced and the rapid development of anemia is more characteristic of either than of acute rheumatoid arthritis. The appearance of an aortic diastolic murmur in this case would suggest the development of an ulcerative endocarditis of the aortic valve. However, no peripheral signs of aortic insufficiency developed and the appearance of such murmurs without the peripheral signs of aortic insufficiency are not uncommon in long standing hypertension such as this patient has.

Acute Rheumatic Fever—One seldom, if ever, sees the initial attack of rheumatic fever at this patient's age. However, not only did she have an acute polyarthritis fifteen months before this admission but gives a history of vague joint pains since the age of eleven. When the initial attack occurs at a young age it is not uncommon to see recurrences in the third and fourth decades of life and commonly anatomical evidence of activity of the infection is present even when the patient succumbs to the cardiac manifestations of the disease. Such severe joint reactions are less often seen in this climate but are not unknown. However, the prompt response of such joints to salicylates is most characteristic of rheumatic fever. Such a response

was obtained in the previous attack but was so delayed in this attack as to create considerable doubt as to its nature. It eventually occurred in characteristic fashion and is strong evidence in support of the diagnosis of rheumatic fever in this case. After repeated attacks of rheumatic fever, although the joint manifestations may be slight one would expect to find definite evidences of rheumatic valvular heart disease. The rough systolic murmur, thought probably to originate at the pulmonary valve was the only suggestion of valvular heart disease until late in her course and this murmur would in no way suggest mitral disease. The heart is somewhat enlarged but a hypertension has been known to have been present for some time and there is nothing in the shape of the heart shadow in the teleoroentgenogram to suggest dilatation of the left auricle or the pulmonary conus. The presence of an old rheumatic valvular heart disease would not exclude other types of joint disease at this time but would establish the presence of rheumatic infection in the past and the tendency to recurrence or exacerbation of this infection would materially increase the likelihood of the present illness being rheumatic fever. Demonstrable evidence of an active carditis at this time would again be strong evidence of rheumatic infection and one would expect to find electrocardiographic evidence of active carditis in so severe an exacerbation of rheumatic fever if such is the case here. This evidence is lacking and the auriculoventricular conduction time is quite within normal limits. Such evidence of active carditis and associated involvement of the pleura or other serious surfaces together with the response of the infection to salicylates is frequently our only means of concluding that an acute polyarthritis is due to rheumatic fever. A high antihemolysin titre is the rule in acute rheumatic fever but it is only confirmatory evidence and does not necessarily differentiate the arthritis from acute rheumatoid arthritis, but is of value in excluding gonococcal arthritis unless there has been a fairly recent streptococcal infection. This property of the serum may be maintained for some time after a totally unrelated streptococcal infection. As we have said, in all of these acute arthritides the sedimentation rate of the red blood cells is elevated and does not aid in their differentiation. However, in acute rheumatic fever the fall in the sedimentation rate and its return to normal tends to lag behind the evidences of clinical improvement, whereas in other types of acute polyarthritis its return

to normal closely parallels the clinical improvement. In this respect it adds confirmatory evidence to the diagnosis of acute rheumatic fever, but requires extended observation to be of value.

This patient, then, presents the problem of the differential diagnosis of acute polyarthritis. The manifestations are not clear cut and leave room for the serious consideration of both acute rheumatoid arthritis and gonococcal arthritis but the weight of the evidence and the subsequent course (the case was presented in clinic before any response to salicylates had occurred), points with a high degree of probability to the diagnosis of acute polyarthritis with rheumatic fever.

Infectious Diseases

Tuberculosis

THE RESOLUTION OF FIBROCASEOUS LESIONS IN PULMONARY TUBERCULOSIS

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THE teaching that pulmonary tuberculosis heals only by fibrosis and calcification must be revised in the light of animal experimentation and roentgenology. The complete resolution of large areas of tuberculous disease in animals and the disappearance of extensive shadows cast on the roentgenogram by pulmonary tuberculosis in man can lead to but one conclusion, namely, that many foci of tuberculosis may resolve and that not every focus of the disease heals by fibrosis.

For many years research workers have found that tuberculous lesions in laboratory animals may, under certain circumstances, regress and disappear. By sacrificing pairs of animals at frequent intervals and comparing the extent of the tuberculosis in the so-called immune animal with its control animal they have found an increasing amount of disease in the control, while in the "immune" animal the tuberculosis recedes and if the animal is allowed to live a year or two little or no tuberculosis may be found. There was always a doubt that the animal which was allowed to live ever had as extensive tuberculosis as was found in the animals sacrificed in the earlier stages of the experiment. The roentgen ray has solved this question, for by serial roentgenograms of the lungs of infected animals one can follow from the first appearance of abnormal shadows the changes in the size, density and distribution of the pulmonary lesions although the roentgenogram does not provide evidence of the exact nature of the underlying pathology which produces these changes. Coincident with the disappearance of abnormal shadows from the roentgenogram

the lungs have shown little or no disease, and Burke's¹ experiments demonstrate conclusively that in rabbits extensive fibrocaseous tuberculosis may resolve.

In man tuberculosis of the lungs may undergo astonishing changes, a fact which was not fully appreciated until the advent of the roentgen ray. These changes in the lesions may be gauged by the shadows which they cast in serial roentgenograms. The shadows of widely distributed areas of bronchopneumonia may rapidly disappear but often these densities persist for many months before they vanish. Studies of the underlying pathology show that an acute tuberculous bronchopneumonia may resolve before necrosis, caseation and cavitation take place, but usually the initial stage of engorgement and exudation passes rapidly into the stages of red and then grey hepatization in which multiple areas of necrosis and caseation appear diffusely distributed throughout the involved area. Caseation and liquefaction may take place terminating in cavity formation. The inner layer of a freshly formed cavity is composed of necrotic tissue in which tubercle bacilli are very abundant. This layer fuses without definite demarcation with a zone of granulation tissue which represents the earliest stage of fibrosis or repair. The walls of older cavities exhibit a layer of granulation tissue surrounded by a fibrous wall in which may be found scattered or extensive areas of caseation. Whether the cavity walls be thick or thin the same elements make up their composition but in varying degrees.

It is generally accepted that the acute tuberculous inflammations may undergo resolution but it has been a traditional concept that caseation and fibrosis do not resolve. Current opinion with a few exceptions upholds this view. To quote from a few authors Aschoff² believes that caseation means destruction of the lung structure which obviously can never be restored intact, and that caseous matter is not absorbed. Krause³ states that "tuberculous processes heal by fibrosis or resolution. It is only the over-plusage in tuberculous pneumonia or the very minutest points of inflammation that do not go on to tubercle that heal, at least partially by resolution. Real tuberculous processes heal by fibrosis" and usually leave their scars, though the old dictum 'no tuberculosis without its scar' is

* Italics mine

undoubtedly false" Amberson⁴ says that "perifocal inflammation may resolve, but the caseous nucleus usually persists indefinitely"

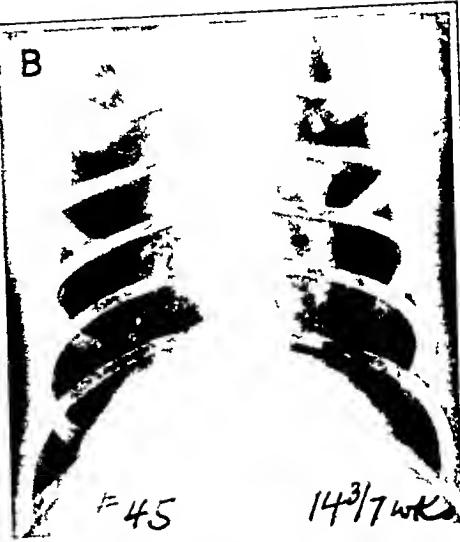
The observations of Gardner⁵ on the fate of the tubercle produced by R1, an attenuated stain of tubercle bacilli, in the guinea pig's lung is well known. By serial examinations of a large number of animals he demonstrated the steps in the development of the tubercle and its progression to caseation, and then the retrogressive stages and eventually the complete disappearance of the focus, leaving the lung intact. During the process of resolution the tubercle slowly shrank in size, its caseous center became smaller and smaller and the surrounding air cells dilated. Finally only a lymphoid deposit was seen and this soon disappeared, and the site of the former tubercle was occupied by normal lung structure. The original tubercle must have destroyed many air cells. Burke's animal experiments have established the fact that large areas of fibrocaseous disease may resolve. In many instances not even microscopic evidence is left to indicate the presence of the former tuberculous inflammation.

I am privileged to show two of the illustrations taken from Burke's* work on experiments in resolution. Rabbit #45 and Rabbit #84 (two animals from a large series) were first sensitized in the groin with 5 cc of a heavy suspension of attenuated tubercle bacilli (R1). Three weeks later they were inoculated intratracheally with 1 mg of virulent human tubercle bacilli (H37). The suspension was allowed to run down into the left lung. Roentgenograms were taken at short intervals and the animals sacrificed at the time indicated in the illustrations. Note in Rabbit #45 the extensive fibrocaseous lesions and cavity formation. Rabbit #84 was allowed to live for over a year. It exhibited the same type of abnormal shadows in the roentgenograms as did Rabbit #45 in the early weeks of the experiments, but as time went on these shadows disappeared and figures E and F show the complete disappearance of lesions from the lungs.

In man the evidence of the resolution of fibrocaseous lesions is offered in the following cases.

CASE 1—J. L. The patient, a physician thirty three years of age, was perfectly well up to the first week of March, 1930, when he developed cough, expectoration, fatigue and temperature of 100°. During the following two weeks his symptoms became aggravated and the temperature rose to 103°. Examination of the chest showed scattered rales in the upper third of the right lung. A

* Plates IV and IX Dr Hugh E Burke, *Am Rev Tuberc*, 32 343, 1935

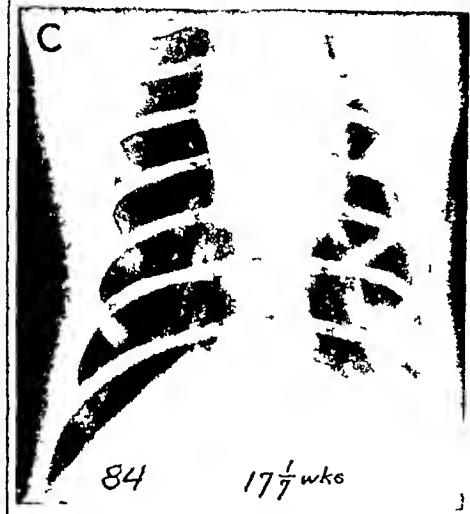
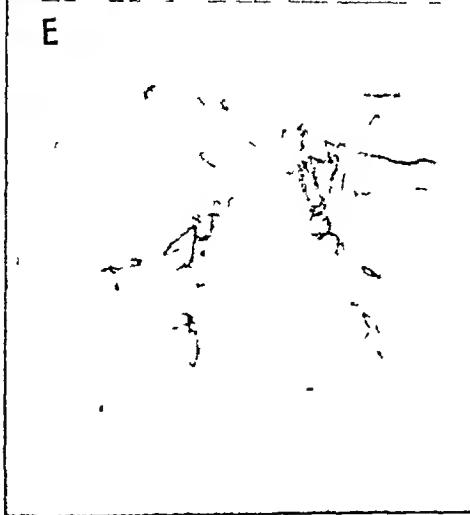


Rabbit No. 45

A Film at 8 2/7 weeks Homogeneous shadows with indefinite margins
 B Film at 14 3/7 weeks Abnormal shadows smaller and denser
 C Film of excised lungs Coarse mottled shadows stippled with minute dense shadows and
 D Photograph of section Multiple fibrocaseous lesions and cavity
 E Fibrocaseous lesions adjoining cavity wall $\times 6$
 F Calcreous deposit in fibrocaseous lesion $\times 100$



3 DAYS

5 $\frac{4}{7}$ WKS84 17 $\frac{1}{7}$ wks84 56 $\frac{3}{7}$ wks

Rabbit No. 84

A Film at 3 days Homogeneous shadow with indefinite margins left lung field
 B Film at 5 4/7 weeks Extensive irregular shadows left lung field
 C Film at 17 1/7 weeks Faint homogeneous shadows, left lung field
 D Film at 56 3/7 weeks No abnormal shadow
 E Photograph of section No macroscopic lesions
 F Portion of left lower lobe Only abnormally thick septa X 60

roentgenogram (fig 1) taken on April 4, 1930, one month after the onset of symptoms shows a dense shadow involving the upper and outer portion of the right lung, its lower border clear cut and located at the 3rd rib anterior, corresponding to the interlobar fissure. There is a round area of rarefaction 3 cm in diameter located in the 2nd interspace. Both hilar shadows are enlarged, particularly the right one. The sputum was positive for tubercle bacilli.

The patient was kept in bed and the symptoms gradually subsided. A roentgenogram (fig 2) taken five months later still shows the dense shadow but its lower border has moved upward an interspace and the cavity cannot be made out. Figure 3 shows the appearance of the lung by roentgenogram taken seven months after the previous film. The dense shadow has now disappeared and no evidence of the cavity is present. There is a small density in the outer 2nd interspace, the lower border is sharply defined and runs downward toward the hilum. A film (fig 4) taken two years after the onset of symptoms shows almost complete disappearance of the shadows originally seen. A small poorly outlined density lies back of the 2nd rib. The hilar shadows on the left appear normal, whereas the right hilar shadow is slightly larger and denser than normal. At this time only a few fine rales were heard at the right apex anterior. The sputum, which was negligible in amount, was negative for tubercle bacilli. The patient is perfectly well and is engaged in full time practice.

Comment—This patient's disease evidently began as an acute tuberculous pneumonia which involved the upper right lobe, but the first roentgenogram (fig 1) which was taken one month after the onset of symptoms shows that excavation had taken place. Tubercle bacilli were found in the sputum. The presence of a cavity definitely indicates that caseation and liquefaction necrosis had developed in the pneumonic area. The wall of this cavity must have been composed of granulation tissue, caseous foci and fibrous strands. Absorption of the inflammatory products of the disease caused the lobe to shrink as is evidenced by the elevation of the interlobar fissure. This shrinkage probably aided in the closure of the cavity. The contiguous normal lung tissue in the lower and middle lobes dilated to compensate for the loss of lung volume in the upper lobe. As a result of resolution the shadows in the upper lobe disappear and the final roentgenogram shows, with one or two exceptions, an apparently normal lung field. The patient is restored to perfect health.

That much of the disease in this patient was of a fibrocaseous nature is shown by, (a) the length of time the dense shadow persisted—four months and longer which placed the tuberculous lesion in the chronic fibrocaseous stage far beyond the acute pneumonic stage, (b) by cavity formation which predicates caseation and liquefaction necrosis and (c) by the presence of tubercle bacilli in the sputum.

which many believe appear only after caseation has occurred. Yet practically all the abnormal shadows including that of the cavity disappeared from the roentgenogram. It is unreasonable to assume that all of the products of the tuberculous inflammation were eliminated by way of the bronchi. It seems evident that the greater part—including areas of caseation, and fibrocaseous disease were absorbed. Fibrous strands, fibroid tubercles and shrunken foci of caseation, encapsulated, or inspissated, doubtless still exist but too small to be visualized on the roentgenogram. But for every focus that remains many times the number have completely disappeared.

The second case illustrates the process of resolution in a patient with chronic fibrocaseous tuberculosis with cavitation.

CASE 2—C F. The patient, a plumber, was twenty six years old when first seen by me in May, 1927. He had always been well. In January of the same year he noticed fatigue, cough and expectoration. He kept at work and quit only three days before coming to Saranac Lake. The day before he stopped work he helped to install thirty radiators in a building. When I first saw him he was ten pounds below his usual weight. He had no fever and his pulse was normal. He had had some night sweats, was somewhat short of breath, and had a moderate amount of cough and expectoration, which was positive for tubercle bacilli. The chest examination showed impaired resonance over the upper half of each lung. The classical signs of cavity formation were present on both sides above the 2nd rib and 4th spine. There were numerous moderately coarse rales heard over the front of the chest and to the 7th spine bilaterally distributed. Figure 5 shows the roentgenogram taken soon after the patient arrived. Mottled densities are seen scattered throughout each lung field. There are two large cavities located above the 2nd rib on each side. There is a fluid level in each cavity.

The patient was kept in bed for a few months. He was then allowed to be up and about because of the disappearance of all symptoms except slight cough and expectoration. He gained rapidly in weight and at the end of October, 1927, he was given walking exercises. Although the cavities were not completely closed at this time, he had no cough nor expectoration. His recovery was without incident and at the end of two years he was discharged from my care. Figure 6 shows the condition of the lungs as revealed by the roentgenogram at this time. The large mottled shadows have disappeared and only a few, very small densities are seen scattered through the lung fields. The cavities have vanished and only a small hazy shadow remains behind each clavicle to mark their sites.

Physical examination at the time of his discharge showed no evidence of cavity formation. A few fine dry rales were heard at the extreme apex on each side anteriorly.

Comment—The mottled densities scattered throughout both lung fields as observed in the first roentgenogram of this patient represent in all probability foci of caseation or tubercle formation. A great

FIG. 1



FIG. 2



Case 1 Roentgenogram taken April 1930 one month after onset
of symptoms Note dense shadow right upper lobe and cavity

1930)

Case 1 Roentgenogram taken five months later (September
1930) Dense shadow still present but cavity not visible

Case 1 Roentgenogram taken April 1930 one month after onset
of symptoms Note dense shadow right upper lobe and cavity

Fig. 3



CASE 1. Roentgenogram taken April 1931. The extensive lucency in the 2nd intercostal space has disappeared, but a small density in the 2nd intercostal space remains.

Fig. 4



CASE 1. Roentgenogram taken two years after onset of symptoms. Only a small density behind 2nd rib and a few markings remain.

FIG. 5



FIG. 6



Case II Extensive bilateral chronic fibroscinous tuberculous infiltrates with fluid levels in upper 3rd of each lung. Large

Case II Radiograph taken twenty-eight months later. Marked disappearance of mottled shadows. No evidence of cavity formation.

Fig 7

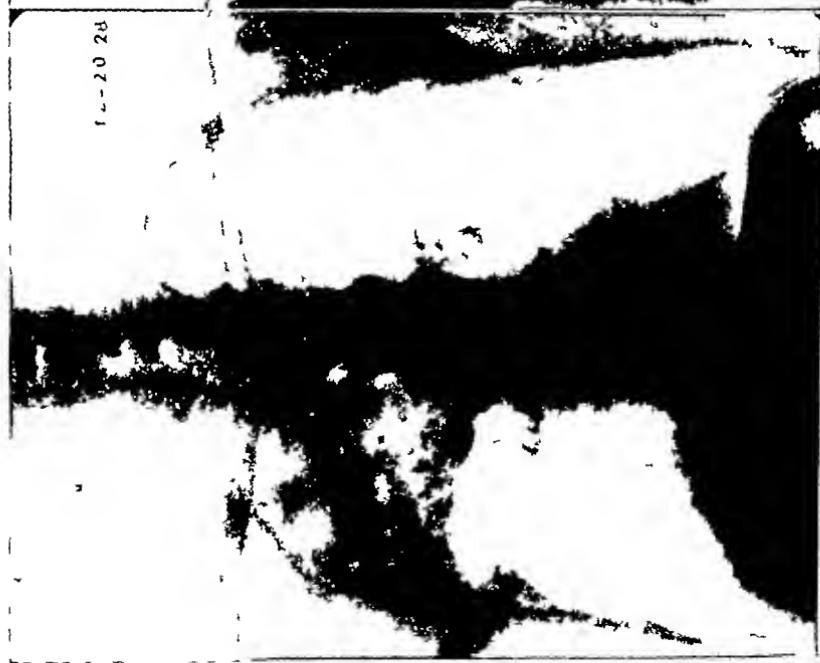
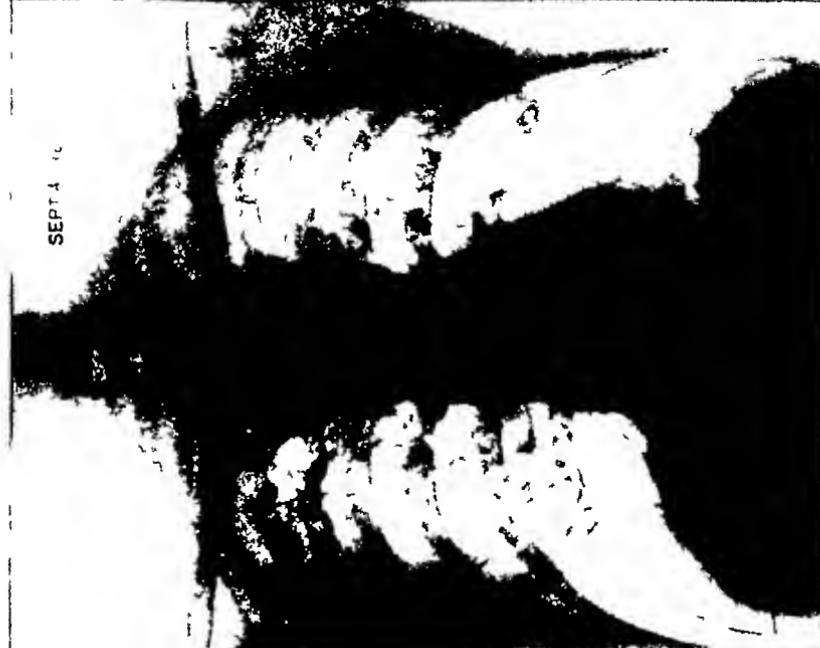


Fig 8



Case III August 13, 1936 Marked contraction of tuberculous process
No evidence of cavity scattered calcified densities throughout both lungs

Case III Extensive tuberculous of right upper lobe with large cavity format on Roentgenogram taken December 20, 1928

number of these densities have completely disappeared from the later roentgenogram. Other foci became encapsulated or fibrous throughout and shrank leaving the small densities seen in the final roentgenogram. The cavities were chronic cavities. Their walls must have been composed of fibrocaseous tissue. Yet by physical examination they are no longer present, and the roentgenogram fails to reveal any evidence of cavity formation.

There is unanimity of opinion that healed cavities leave scars. These may be but narrow bands of fibrous tissue which are not typical and do not indicate their origin from a cavity. Unless we assume that the cavity walls were expectorated we can come to no other conclusion than that resolution of most of the fibrocaseous matter has taken place. The healthy air cells have dilated and occupy the space of the former cavities.

The third case illustrates the processes of resolution, fibrosis and calcification which took place over a period of years.

CASE 3—H C. The patient, a male twenty nine years of age gave a history of dry pleurisy in 1917. He was below par at that time and was refused enlistment by a Draft Board. He worked steadily until October, 1928, when he developed a bronchopneumonia. He had pains in his right chest, fever to 104°, cough, expectoration, and loss of weight. The sputum was positive for tubercle bacilli. A roentgenogram of the chest at that time showed a dense shadow occupying the upper half of the right lung field. Figure 7 is the roentgenogram taken ten weeks later. It shows a dense mottled shadow in the upper half of the right lung. Its lower border is clear cut and is located in the 3rd interspace. A large area of rarefaction is seen above the 3rd rib and extends almost to the apex of the lung. There is a narrow dense homogeneous shadow at the periphery of this area and it extends upwards over the apex. There are mottled shadows seen from the root to the base.

This patient evidently had in 1928 an acute exacerbation of a chronic tuberculosis. That the lesion is not entirely a recent one is shown by the marked densities seen within the mid lung on the right, the deviation of the trachea, the pleural thickening and the narrowed interspaces in the upper 3rd of the chest on the right side. The left lung field is clear.

The physical examination of the chest showed on the right side dullness to the 3rd rib and 5th spine. In this area there was very marked bronchovesicular breathing, and increased vocal resonance and a few moist rales. At the left apex there was impaired resonance, bronchovesicular breathing and an occasional rale.

With bed rest the symptoms subsided and the patient gradually returned to good health so that he has been able to carry on a business and to engage in numerous civic duties.

A moderate amount of cough and expectoration have persisted and the sputum remains positive for tubercle bacilli.

During the intervals between 1928 and the present day there has been a gradual shrinkage of the process in the right lung so that now (fig 8) we see a small dense shadow occupying the extreme apex of the right lung. No definite cavity can be made out. There are string like shadows and scattered densities throughout the right lung, some of which appear calcified. In 1929 fresh disease appeared in the left lung which accounts for the shadows seen in figure 8. In August, 1936, the chest examination showed dullness to the 2nd rib and 4th spine, bronchial breathing and whisper and a few dry squeaks in the same area. No rales were heard in the left lung.

Comment—This patient exhibits a combination of acute and chronic tuberculosis with large cavity formation. The pathological picture is one of pneumonic tuberculosis associated with fibrocaseous disease and excavation. A combination of repair processes were operative in bringing about the final state of fibroid tuberculosis and calcification. I believe that much of the pneumonia resolved and at the same time the whole upper lobe shrank, and the cavity walls were approximated. Fibrosis formed and as a result the lobe became a small fibrous mass occupying the extreme apex of the left lung. To compensate for the loss of lung volume the middle and lower lobes dilated and the mediastinum and trachea moved over. Resolution, fibrosis and calcification took place in the scattered areas in the other parts of the lungs.

The marked shrinkage of the upper lobe may have been caused by an occlusion of the bronchus to that lobe and as a result the air distal to the stricture was absorbed and the lobe collapsed. This caused the cavity walls to contract and the antrum was obliterated. Within the diseased upper lobe much caseation must have been present. The cavity walls alone probably contained numerous caseous areas. What has become of these foci? Are they all still present in the apical scar? No doubt some of them are there to-day but I believe that much of the caseation and fibrous tissue resolved.

It will not be necessary to give all the details of the long course of the fourth illustrative case.

The patient was a young woman twenty nine years of age who presented herself with advanced fibrocaseous tuberculosis with cavitation involving the left lung (fig 9). The cavity measured 3 by 4 cm. The sputum was positive for tubercle bacilli. Artificial pneumothorax was established on the left side. The collapse was not satisfactory and pneumolysis was performed. A few months later fresh disease appeared in the middle and lower portions of the right lung and a large cavity developed (fig 10). Pneumothorax was instituted on this side and carried on for many months, the left lung meanwhile slowly re-expanding.

FIG. 9



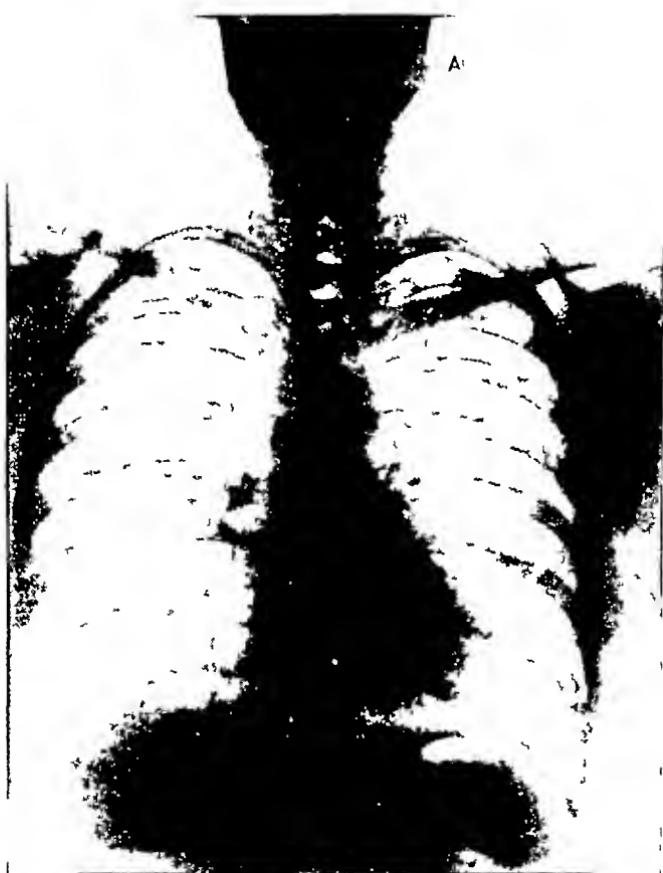
FIG. 10



Case IV Extensive chronic tuberculosis of left lung with cavity in upper 3rd March 26 1931

Case IV Artificial pneumothorax, left. Development of large cavity right lower lung. Thus lung was also collapsed by artificial pneumothorax June 17 1932

FIG. II



Case IV Three years after reexpansion of both lungs. No evidence of cavity formation in either lung August 4 1936

Eventually the right lung is expanded. The sputum became negative for tubercle bacilli, and although the patient still has daily expectoration it has contained no bacilli for a period of three years. Figure 11 shows the condition of the lungs to day as revealed by the roentgenogram. No trace of the cavities can be seen. If the lungs could now be sectioned, doubtless numerous residual foci would be found but during the years of collapse therapy many of the fibrocaseous lesions must have resolved.

DISCUSSION

The disappearance from the roentgenogram of shadows cast by pulmonary tuberculosis has been observed by others innumerable times. The resolution of the acute (exudative) forms of tuberculous pneumonia has been advanced to explain this phenomenon. Such lesions may be widespread or they may be small such as the zones of acute inflammation which some maintain surround tuberculous foci. But when the time element is considered in these cases it is often found that many of the shadows have persisted for many months or even years before they vanished. The patients were not acutely ill but were generally quite well although they may have had extensive bilateral tuberculosis with cavitation. The underlying pathology of these chronic cases is predominantly a fibrocaseous type. Acute exudative inflammation is surprisingly absent. The alveoli not directly involved with caseous or fibrous material contain mononuclear cells and lymphocytes and a few fibrous strands—a chronic inflammation. Yet in many instances these lesions, including cavity formation, may disappear as judged by roentgenological and physical examinations.

Granting that resolution may occur there are differences of opinion as to how large an area of caseation may resolve. In Gardner's experiments the tubercle with its caseous center was very small yet compared with the diameter of an alveolus the tubercle occupied the space of many air cells. Yet it disappeared and the normal lung dilated to compensate for the destroyed alveoli. In Burke's animal experiments we find much larger areas—parts of or even whole lobes involved with fibrocaseous lesions, and even these resolved. In man there is the roentgenological and physical evidence that very large areas of chronic tuberculosis with cavity formation may disappear.

An apparently normal roentgenogram of the lung fields does not mean that there are no foci remaining in the area previously involved with disease. The dilated air cells which compensate for lost tissue

may facilitate the penetration of the roentgen ray so that scars and other densities may not be visualized on the film. Sweany⁶ states that only "approximately half of the calcified parenchymal lesions may be seen on ante mortem radiographs." This does not contradict the statement made earlier in the discussion that for every focus that remains many times that number have disappeared.

One may argue from analogy and point to the absorption of caseous material in tuberculous glands, bones, or joints. A peritoneum studded with tubercle may return to its normal glistening state. The absorption of scar tissue in various parts of the body is well known.

In the light of animal experimentation, and the roentgenological and clinical evidence in man, I do not see how we can escape the conclusion that fibrocaseous lesions may resolve and leave no trace behind.

I wish to acknowledge my indebtedness to Doctors Bay and Burke of the New York State Hospital, Ray Brook, and to Doctors Gardner and Vorwald of the Saranac Laboratory for helpful criticism and advice.

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HAEMATOGENOUS TUBERCULOSIS

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THAT the tubercle bacillus is disseminated by the blood stream is a fact that requires no extended demonstration. The obvious forms of miliary tuberculosis have been recognized since the cause of tuberculosis was first known. The question, however, of how large a part of this haematogenous spread plays in the total picture of the development of tuberculosis is not so clear and, in all probability, has not received the attention its importance warrants. Tuberculosis may spread by contiguity from the original focus as has been shown by Ghon in his study of cavity formation in infants,¹ or in adults, as an exacerbation of old sharply localized lesions.² The spread may be through lymph channels as in the primary types of lung lesion, with involvement of regional lymph nodes, or intracanalicularly through the bronchial tree and the intestinal tract to the vast surfaces thus exposed, over the free spaces of serous cavities, pleura, peritoneum, or meninges, or, lastly, through the blood stream.

The relationship between infection and the dissemination resulting in clinical disease needs further study. We know that most of our adult population is infected with tuberculosis. We also know that not more than 5 per cent die of tuberculosis. In New York State, for example, there were, in 1934, 149,000 deaths from all causes, and of these 7,500 were from tuberculosis. To hope soon to eliminate infection is quite Utopian. It is important, however, to understand as clearly as possible the various steps between infection and manifest disease. We must also eventually understand more clearly the relationship between exogenous re-infection and endogenous re-infection, for on this will depend our attitude toward tuberculosis as a public health problem and the best methods of control. The relative importance of various methods of spread within the body is a small part of this problem. It is our belief that the haematogenous spread plays a much larger part in tuberculous disease than is usually appreciated and that the more we look for evi-

dence of this method of spread the better we shall understand and manage clinical disease, and the less emphasis we shall place on exogenous re-infection as a cause of recurring disease

How often does the tubercle bacillus appear in the blood stream? Undoubtedly it occurs much more frequently than does typical miliary tuberculosis. In experimental guinea pig disease bacilli have often enough been found in the blood but tend to disappear rather rapidly. In human disease findings are much less frequently positive. Villemin, as early as 1866, infected guinea pigs with blood from tuberculous patients. Figures of later investigators have varied within wide limits. Leibermeister,³ for example, found bacilli in two of eighteen Stage I, fourteen of fifty-two Stage II, twenty-four of fifty Stage III pulmonary cases, as well as in some patients who did not have clinical disease. These figures and many other similar ones are based on results of microscopic examination of blood cultures or even blood smears, and are open to error because of possible contamination with other acid-fast bacilli often shown to be present in laboratory materials, or brought in by cultural methods. We must require evidence of animal pathogenicity and accept such reports as those of Steiger⁴ who found in ninety-five cases two positive, both of which later developed extrapulmonary tuberculosis, and Corper⁵ who studied by three cultural methods and guinea pig inoculation one hundred and twenty pulmonary cases with entirely negative results. He concluded that "embolic showers may occur but, when they do, are rapidly removed from the circulation in the usual case of tuberculosis."

Mention should be made here of the work of Lowenstein, not because of its conclusive value, but because it caused a greatly renewed interest in the subject and led to a great deal of more critical work by others. He reported the finding of tubercle bacilli by culture in 40 per cent to 100 per cent of frank pulmonary tuberculous cases, and also in cases of skin tuberculosis, polyarthritis, chorea, schizophrenia, and other conditions. His reports led to a critical investigation of the whole subject by G. S. Wilson⁶ for the Medical Research Council of Great Britain. Schwabacker in this report obtained by animal inoculation five positive results in two hundred and eighty-two living cases. In critical estimate of all work Wilson gives the following summary which is the most reliable available:

| Type of Disease | No of Cases | No Positive | Per cent Positive |
|---------------------------------------|-------------|-------------|-------------------|
| Pulmonary tuberculosis, mostly severe | 680 | 33 | 4 9 |
| Miliary and meningeal tuberculosis | 22 | 8 | 36 4 |
| Non-pulmonary tuberculosis | 222 | 6 | 2 7 |
| Tuberculosis—undefined | 325 | 9 | 2 7 |

All such reports are, however, based on a few examinations in any one individual. It must be granted that bacilli may have been present for brief periods of time in a much greater percentage. To establish such a fact it would be necessary to follow individual cases repeatedly over a long period of time. No one has yet done this.

In a discussion of haematogenous tuberculosis mention should also be made of the work of Ranke¹. He constructed a three-stage sequence of events in tuberculosis analogous to infectious disease in general and especially to syphilis. His theory postulates a first stage or primary complex which spread by lymphatics, a secondary or generalized stage disseminated mainly by the blood stream, and a third stage of localized disease in various organs or tissues spread intracanally, i.e., by the various open passages of the body—the bronchi, urinary tract, etc. In these stages he also brought in various immunological and allergic accompaniments which helped explain the varying manifestations. These are too involved to discuss in this paper. Careful investigators, Schurmann² and others, while admitting the stimulating effect of his concept, have had difficulty correlating his ideas in detail with postmortem findings. The difficulty is due largely to the fact that the terminal stages are so involved that it is hard to trace the complete story. His ideas are of value in emphasizing the large part often played by the blood stream, whether we can clearly differentiate this as a second stage or not. Also, in a general way, his idea of system disease in the third stage is borne out by clinical observation. Pulmonary disease of classical type is apt to progress without extensive involvement of other organs except those directly reached by the canalicular system, and the extrapulmonary lesions are apt to be accompanied by relatively benign pulmonary lesions which are a part of a generalized tuberculosis.

The most obvious evidence of blood stream infection is the finding postmortem of tuberculous lesions in organs or tissues which can be reached only by the blood stream. Though most tuberculous deaths are due to pulmonary lesions, extrapulmonary lesions to some degree

are found in nearly every case. In going over the autopsy material of tuberculosis cases for the past five years at the Albany Hospital, the following distribution of lesions was found.

TABLE I

| No. of patients | 170 |
|-------------------------------|-----|
| Lesion primary in lung | 154 |
| Lesion primary in bone | 3 |
| Lesion primary in gland | 1 |
| Acute miliary | 12 |
| <i>Secondary Lesions</i> | |
| Intestines | 97 |
| Spleen | 96 |
| Liver | 88 |
| Kidney | 41 |
| Glands | 40 |
| Adrenals | 25 |
| Peritoneum | 22 |
| G-U tract (other than kidney) | 22 |
| Pancreas | 6 |
| Heart | 4 |
| Bone | 4 |
| Brain | 2 |
| Esophagus | 1 |
| Thoracic duct | 1 |
| Gallbladder | 1 |

The number of different tissues involved in each case was as follows:

| | |
|---|----------|
| Lung only (including bronchial glands and pleura) | 13 cases |
| 2 tissues involved | 22 " |
| 3 " | 21 " |
| 4 " | 23 " |
| 5 " | 29 " |
| 6 " | 27 " |
| 7 " | 12 " |
| 8 " | 8 " |
| 9 " | 5 " |
| 10 " | 3 " |
| 11 " | 1 " |
| <hr/> TOTAL | 164 " |

Two classes of lesions are not included in the above summary—laryngeal, because the larynx was not systematically examined at

autopsy, and pleural lesions, because they are practically always present in cases of pulmonary tuberculosis

Such a compilation is admittedly incomplete. A more detailed pathological study would undoubtedly have revealed many lesions not reported in these routine autopsies. It is sufficiently complete, however, to demonstrate that blood stream infection occurs to some extent in nearly every case of tuberculosis. It is also evident that at least some of the lung lesions of advanced pulmonary tuberculosis are of haematogenous origin.

It is in these lung lesions that we are particularly interested in this discussion. It must be admitted, first of all, that absolute proof of the haematogenous origin cannot be presented. Even in typical miliary tuberculosis this would be difficult. There are, however, certain characteristics of this type of case that differentiate it from the usual bronchogenic type of tuberculosis. These are the uniform, even distribution of lesions of about the same size throughout the lung field, the frequent occurrence of lesions of tuberculosis in other parts of the body which are obviously infected only through the blood stream, and the absence of old pulmonary disease from which dissemination could take place in the usual bronchogenic manner.

At the one extreme we have typical miliary tuberculosis. This disease, beginning as an acute illness and progressing in a few weeks to death, and with widely scattered lesions of uniform density, is clearly understood and will not be further discussed here. This type has been eliminated from the cases selected for this study. There are, however, other groups of cases in which the previously mentioned characteristics are present but which are much more protracted in their course and at times progress to recovery. It is admittedly difficult to differentiate sharply many of these cases. In the first place, in tuberculosis of a prolonged course, the original picture may become obscured by later developments. Though the fundamental lesion may be haematogenous there may be a rupture at some point into the bronchial tree and a true bronchogenic lesion be imposed on the earlier lesion. Secondly, a real haematogenous lesion may be superimposed on an old bronchogenic one. In fact, this is a very frequent occurrence. In over half of the cases we studied this was the case. Preceding the terminal illness, there were apparently one or more crops of blood-borne disseminations and it was these and not the

chronic disease that caused death To judge in all cases exactly how much of the lesion is of one type or the other is impossible We can only approximate the truth

The forms of haematogenous pulmonary tuberculosis, exclusive of the acute miliary form, have received much more attention abroad than in our country French literature has long been pervaded with this concept Bard,¹¹ in 1901, in his beautiful but rather elaborate classification, described "formes interstitielles ou granulique," which he recognized as haematogenous in origin, and that they were often accompanied by extrapulmonary lesions, were relatively benign, and gave few signs or symptoms With great clinical perspicacity and without roentgen ray studies, he recognized their association with certain forms of diffuse fibrosis Since then, many other French writers have elaborated greatly on these forms German writers were greatly stimulated by the work of Leibermeister and especially of Ranke It was Schurmann who first introduced the term "chronic protracted haematogenous dissemination," which quite accurately defines the forms we are most interested in here Relatively little attention has been paid to them in American literature Only since 1934 have the articles of Miller,⁸ Pinner,⁹ and Reisner¹⁰ and others appeared

ROENTGENOLOGICAL PICTURE

The haematogenous character of this type of tuberculosis is generally first suspected by the appearance of the roentgenogram As the peculiar characteristics are apt to be submerged by other forms of dissemination if death occurs, and as the healing case does not come to autopsy, or at least till the most characteristic lesions are changed, we must rely strongly on the serial study of roentgenograms

These lesions appear as widely scattered, rather symmetrically distributed nodular densities They are not uniform in size and have rather poorly defined borders, and are not associated with a definite large focus in the lung as are bronchogenic types The more chronic the nature of the disease the more the character of these foci vary as the development is dependent on succeeding crops of tubercle bacilli seeded into the lung As the process becomes old, the lesions become more clearly defined, and a stringy lace-like network becomes apparent between the lesions This is evidence of the diffuse interstitial

fibrosis which accompanies the healing process. In the end, little may remain of obvious infiltration and only a fine network of thin lines remain. Sometimes the fibrosis is so fine that it is not revealed by the film.

Another characteristic in older lesions is the presence of widely scattered calcified foci. This is a highly characteristic feature, as has been observed by Pinner⁹ who states that after examination of thousands of roentgenograms calcification occurs only in true primary foci and in lesions presenting characteristics of haematogenous type.

Another characteristic emphasized by German writers, but not so generally agreed upon, is the "Lochkaverne" or "punched out" cavity. Such cavities are shown as thin-walled ring shadows, lying in quite normal looking lung tissue. They do not have the heavy indurated wall of bronchogenic cavities and may remain unchanged over long periods of time without giving rise to spread of the tuberculous process.

As will be shown by cases later, the differentiation between true miliary tuberculosis and these more chronic forms cannot be sharply drawn. One type shades into the other. Also, other types of dissemination may be superimposed on the haematogenous so that interpretation of the roentgen ray picture may be at times quite complex.

CLINICAL CHARACTERISTICS

The outstanding characteristic of this group clinically is the lack of symptoms. There may be malaise, loss of weight, nervous irritability or digestive disturbances, but often few symptoms are present. Pulmonary symptoms, cough and expectoration, may be entirely absent. Physical signs as well may be entirely absent and the discovery of the disease may be made only by an accidental or routine roentgen ray film. Tuberle bacilli are absent from the sputum, or very scanty, and probably mean that the lesion has broken through at some point from interstitial tissue to the bronchial tree. So marked is this feature that widespread calcifications may be detected by roentgen ray without the person having knowledge of any illness. Another characteristic often noted is the occurrence of frequent and small haemoptyses. In fact, this feature may make us suspect the nature of the illness before the roentgen ray reveals definite characteristics.

This mild clinical course and lack of pulmonary symptoms may

make the diagnosis difficult. When the lesions are small one must differentiate from acute miliary tuberculosis. The lesions of chronic haematogenous type are generally larger, more varied in size, and less sharply defined. It may be necessary to follow the progress of the disease before one can be sure of what one is dealing with. A diagnosis of pneumonoconiosis may be made and discarded only when the lesions clear. Metastases of malignant disease may be indistinguishable from the larger nodules of haematogenous tuberculosis, and in any case rigid investigation of such a possibility must be made and a period of observation may be required before a conclusion is reached.

The relation of this disease to forms of pulmonary fibrosis of indefinite nature is an interesting one. We often see individuals with evidence of old tuberculosis but in whom the symptoms of limited respiratory capacity are out of proportion to the apparent degree of involvement. Knowing as we do that very widespread disease may clear roentgenologically and leave only a fine diffuse fibrosis, it may be that haematogenous tuberculosis is more often the cause of this obscure type of disease than has so far been demonstrated. As Pinner points out, our knowledge of any disease, other than tuberculosis, causing a diffuse fibrosis, is slight. Even though a bronchogenic form of pulmonary disease may be obvious, there is the possibility of there having been at first, or at some later stage, a haematogenous phase leaving little gross evidence of tuberculosis behind. Occasionally this diffuse fibrosis may gradually increase until the embarrassment of circulation and cardiac failure eventually contribute to the death of the patient. One such case of increasing fibrosis is here reported, where the diagnosis of the tuberculous etiology was made only after death, though observation had extended over five years.

PATHOLOGY

The uniform-sized, sharply defined lesions of acute miliary disease are not here considered as we are primarily interested in the more chronic haematogenous forms. We can mention only general characteristics as the picture depends upon the stage of the disease when death occurs. These lesions are seeded in the walls of lymph and blood vessels, tending to leave the intimal lining intact. They

vary in size, show little tendency to coalesce in earlier stages. They give rise to considerable fibrosis of interstitial, interlobular and interlobar tissues. As they heal this fibrosis may so dominate the picture that little characteristic tuberculous tissue remains—the reticular lymphangitis of Schurmann. Areas of emphysema lie between the fibrotic areas. As in the roentgen ray picture, the symmetrical and widely scattered distribution of these relatively small lesions is entirely different from that of bronchogenic disease. Terminal calcification is too widely distributed to suggest primary foci. Another characteristic is the tendency to subpleural localization which may explain the repeated pleurisies noted by French writers as characteristic of this type of disease. The thin-walled, punched out cavities have been previously mentioned. Tissue in the immediate vicinity may be quite normal. As most of these protracted forms lead at some points to bronchogenic dissemination, it is unwise at autopsy to draw conclusions from small areas. One must take into consideration the total picture in conjunction with the preceding clinical development and serial roentgen ray pictures.

CASE REPORTS

The following cases were selected from some 900 consecutive cases as they appeared on the tuberculosis service at the Albany Hospital, all with well defined pulmonary lesions. Cases of acute miliary tuberculosis were eliminated. From the remainder were selected, first, those with well marked and gross extrapulmonary lesions as this was regarded as *prima facie* evidence that important haematogenous dissemination had at some time occurred. As we are primarily interested in the pulmonary manifestations we then eliminated several cases of old bone tuberculosis, and some of glandular tuberculosis in which pulmonary disease afterwards developed.

In addition were selected certain few other cases because they presented outstanding illustrative features though extrapulmonary lesions were lacking. It is not intended that this be a definitive classification of all types found in the 900 cases but more as illustrations of the varying types found in the general group of haematogenous pulmonary tuberculosis. It is impossible to divide this material into sharply differentiated groups but for purposes of clinical discussion

the following subdivisions were made. Illustrative case reports are given

Cases with Definite Extrapulmonary Lesions

| | | |
|-----|--|----------|
| I | Subacute miliary tuberculosis | 3 cases |
| II | Chronic protracted haematogenous tuberculosis in adults | 12 cases |
| III | Chronic haematogenous tubereulosis in children | 4 cases |
| IV | Old pulmonary tuberculosis with terminal miliary dissemination | 18 cases |

Cases without Extrapulmonary Lesions

| | | |
|-----|---|---------|
| I | Healed miliary tuberculosis | 1 case |
| II | Cases with haematogenous lung characteristics but no extrapulmonary lesions | 4 cases |
| III | Repeated pleurisies | 4 cases |

GROUP I SUBACUTE MILIARY TUBERCULOSIS

In this group are found gradations between true acute miliary and chronic haematogenous types. In two cases the picture on admission was that of a miliary tuberculosis with fine, densely seeded nodules throughout the lung. They showed improvement clinically and by roentgen ray film but finally after six months succumbed to tuberculous meningitis. It seems that if this final complication had not occurred, they might have gone on to a healed miliary disease, as is shown in a later case. The third case is reported in more detail.

CASE 1.—Twenty five year old male, waiter. This patient entered the hospital in February of 1933. He gave a history of slight malaise, cough and a loss of fourteen pounds in weight, over a period of four months. In 1929 the right index finger had been accidentally amputated at the middle phalangeal joint. Two weeks before admission, he had squeezed the stump of this finger. It became swollen and tender and was later amputated, revealing a tuberculous osteomyelitis.

Chest examination showed fine and medium coarse rales to the second rib right and throughout the left side and diminished breath sounds throughout the left side. The film revealed a very fine miliary mottling throughout the chest and denser more conglomerate patches on the left.

During the next year, he felt well and had little cough or expectoration but ran an irregular low grade fever, rarely above 100°. A few tubercle bacilli were occasionally found in the sputum giving a Gaffky count of I or II. During his residence of three years he frequently had blood streaked sputum and occasionally frank hemoptyses, usually small in amount but two or three times amounting to five or six ounces. At first the roentgen ray densities on the right increased and later almost disappeared. The densities on the left increased. During the last

FIG 1



CASE 1 Moderately fine nodular diffuse mottling throughout right side. Mottling of same type and diffuse fibrosis on left side. Tuberculous osteomyelitis right index finger. Lesion on right appendectomy almost entirely under observation living four years after onset.

CASE 3 Moderate coarse nodular mottling throughout both lungs. Extensive tuberculosis of terminal vessels and epididymis. Calcified cervical glands. Death one year after onset. Film taken two months before death.

FIG 2



FIG. 3



Case 3 Microphotograph of lung section. Enormous numbers of solitary and conglomerate tubercles throughout both lungs varying in size some quite young others older larger ones showing caseous centers smaller ones showing giant cells and little caseation. Marked scarring of lung tissues.

year of his residence, he had no fever, ten routine sputum examinations were negative, one guinea pig inoculation was positive. He developed schizophrenia and was discharged in March of 1936 to a mental hospital. The spinal fluid was microscopically normal. The blood and spinal fluid Wassermann reaction was negative. He is still living almost four years after the onset of his disease.

Therefore, in this case a fine miliary dissemination throughout one lung cleared markedly while a denser lesion on the other side progressed to fibrosis. A haematogenous skeletal lesion was also present.

GROUP II CHRONIC PROTRACTED HAEMATOGENOUS TUBERCULOSIS IN ADULTS

Of these twelve cases, five will be briefly reviewed.

CASE 2—Forty year old motorman. In 1927, this patient developed pain in the back and was treated for neuritis. In 1931 he began having pain in the right knee, hip and elbow and was treated for arthritis. Two months before admission he had chills and fever and began to cough. Two days before, he had a small hemoptysis. He was admitted to the hospital in May, 1932. Chest examination showed diminished breath sounds throughout and a few squeaky rales at the bases. Chest roentgenogram showed a scattered, moderately coarse mottling throughout both lungs. The sputum was slight in amount but contained tubercle bacilli. Clinical and roentgen ray studies of the bones showed a tuberculosis of the lumbar spine, left elbow and probably of the left knee. These joints were all immobilized and improved greatly except the elbow, which suppurated badly and had to be resected, showing tuberculosis on pathological study. The chest lesion cleared markedly, leaving a diffuse fibrosis. In eighteen months, he had recovered sufficiently to leave the hospital and a year later was quite well and had resumed a light occupation, his main disability being due to mechanical difficulties associated with his bone tuberculosis.

Here we have a widespread haematogenous infection involving several joints and both lungs, with recovery. It seems likely that there had been successive seeding of tuberculosis through the body at varying intervals.

CASE 3—Forty eight year old male, telephone supervisor (figs 2 and 3). This patient entered the hospital in October 1935. Ten months before he had consulted his physician because of slight cough, dyspnoea and weakness. Heart disease was diagnosed. With rest and digitalis he improved and in six weeks returned to part time work. Two months before admission he was again forced to rest. For one month, he had noticed nodular swellings on both testicles. On admission, the patient was well nourished. He was slightly cyanotic and very dyspneic. Medium coarse rales were present on the upper half of both lungs. The roentgenogram revealed a rather coarse nodular mottling throughout both lungs and an old extensive calcification of the cervical lymph nodes. Sputum

was very scanty and contained tubercle bacilli. The epididymis and prostate were enlarged and nodular. He continued to run a low grade fever of 100 to 101 degrees. The pulse rose from 90 to 110, dyspnea increased and he died on October 8, 1935, two months after admission.

The autopsy revealed acute and chronic tuberculosis of the prostate, seminal vesicles, epididymis, and adrenals, miliary tuberculosis of the lungs, liver, spleen and kidneys and a tuberculous ulcer of the ileum. Microscopic examination showed the pulmonary tissues extensively and uniformly infiltrated by enormous numbers of solitary and conglomerate miliary tubercles. Many of these were quite young, while others appeared older. Some of the larger ones showed slight caseation and giant cells. Marked diffuse fibrosis was scattered between these tuberculous lesions. No older pulmonary lesion was found.

We have here an old calcified tuberculosis of the cervical lymph nodes antedating the other lesions, a diffuse haematogenous dissemination throughout the body, most marked in the lungs and genital organs. The terminal illness lasted at least a year.

CASE 4—Male, age thirty nine, chauffeur. This patient gave a history of having had a chronic cough for many years. Two months before admission, the cervical and axillary lymph glands on the right side became very much enlarged. Anorexia and malaise appeared and he was forced to stop work. The cough became very much worse and sputum of a mucopurulent character appeared. He was first admitted to the Surgical Service where a radical removal of the right cervical and axillary lymph nodes was performed. These were shown to be tuberculous on pathological study. Because of an increase in pulmonary symptoms, he was transferred to the Tuberculosis Service. At that time, he had a temperature of 101° to 104°. Sibilant and medium coarse rales were heard at both bases. The spleen was palpable and the liver was four fingers' breadths below the costal margin. A trace of albumin was present in the urine, but no casts were found. A search for tubercle bacilli in the urine was unsuccessful. Repeated smears of the sputum showed no tubercle bacilli but eventually guinea pig inoculation was positive.

Roentgenograms of the chest showed a haziness and ill defined mottling of both bases. Under Sanatorium regime he gained twenty pounds and the operative wounds in the neck and axilla slowly closed, although a fistula still persists in the axilla. In August, 1936, a small, painless swelling developed in the right epididymis which is thought to be tuberculous in character. In August also, the roentgenogram revealed a light, diffuse, fine mottling throughout both lungs. By November this mottling had become more discrete and definite. The patient, however, has gained forty pounds and looks better than at any time since he has been under observation. His temperature and pulse have been only slightly elevated in the last four months.

In this case, there had apparently been a light seeding of bacilli in the lower part of both lungs. Later on extensive acute glandular tuberculosis, then a tuberculosis of the genito-urinary tract and probably, also, additional dissemination in the lungs occurred. These

repeated episodes extended over a period of at least eight months. The patient is handling his varied lesions so far with apparent success. The original focus of this infection has not been determined.

CASE 5.—Female, stenographer, age twenty six. This patient entered the hospital in April, 1934, because of cough, sputum and fever. At the age of eight, tuberculous glands of the neck had been removed. Her right ear had drained intermittently since childhood. Two years before admission a tuberculous kidney was removed. In January, 1934, respiratory symptoms appeared for the first time. On admission her general condition was good. There was slight impairment to percussion to the second rib on both sides of the chest and broncho vesicular breathing and rales on the right to the interspace. The roentgenogram showed a rather stringy mottling above the clavicle and between the second and fourth ribs on the right and below the left clavicle. There was a small cavity in the right apex. The sputum was positive, Gaffky I and II for a month and negative thereafter. The urine was clear. She had no fever or elevation of pulse. There was, occasionally, slight drainage from the ear which failed to show tubercle bacilli on animal inoculation. She made an uneventful recovery, with clearing of the roentgen ray lesion and closure of the cavity, and remains well at the end of three years.

There is little in the objective findings as far as the lungs are concerned that would differentiate this case from a usual case of pulmonary tuberculosis, but the history of various extrapulmonary lesions reveals its haematogenous nature. Proper appreciation of this fact will often be of considerable value in management and prognosis of such cases. Pulmonary symptoms may be absent and the scattered lung lesions may at first clear almost completely, and are thus not followed up carefully, their significance being overshadowed by the presence of gross extrapulmonary lesions.

CASE 6.—Male, factory worker, age twenty four (fig. 4). This man had all his life enjoyed good health, with no history of respiratory illnesses. On August 12, 1936, he accidentally struck his left testicle with a wrench. It became swollen and very painful. This swelling did not subside and when first seen at the hospital, the left epididymis contained several firm nodules, the largest being about two centimeters in diameter. The prostate did not seem enlarged, the urine was normal and there were no urinary symptoms. After a month of observation, the epididymis was removed, three months after the accident. The wound closed, except for a small drainage tract, two months later. Pathological examination showed caseating tuberculosis.

The lung findings were most interesting. There were a few dry medium coarse rales to the level of the second rib on the right, and diminished breath sounds and similar rales to the fourth rib on the left. The roentgenogram showed scattered, irregularly outlined calcifications, one to three millimeters in diameter and fine stringy shadows throughout both lungs. In the upper half of the left

lung these findings were very marked and there were several overlapping ring shadows. This man had no fever except for a few days after operation. He was well nourished and well developed and had lost only a little weight which he promptly regained.

We can only interpret this as a case of old, widespread haematogenous tuberculosis. It seems most likely that there was an old quiescent focus in the epididymis which was reactivated by trauma, in addition to many old foci in the lungs. The other explanation would be that at the time of the accident, or shortly thereafter, tubercle bacilli were present in the blood stream and found lodgement in the traumatized tissue. In view of his excellent general condition and the old appearance of the lesions in the lung, this seems unlikely. The ring shadows probably represent the dry, thin walled cavities found in this form of tuberculosis.

GROUP III CHRONIC HAEMATOGENOUS TUBERCULOSIS IN CHILDREN

Protracted haematogenous dissemination is probably more common in children than in adults. Our service admits few children but a brief mention of this group is made for the sake of completeness. These cases are characterized by pan-adenitis, pan-serositis, roentgen ray evidence of widely disseminated nodules in the lungs and spleen, exudate into, or adhesions of the joints, papulonecrotic tuberculides of the skin or small subcutaneous tuberculous abscesses. The lung lesions may clear, leaving scattered calcification or terminal fibrotic lesion in the upper chest fields. For a complete discussion, the reader is referred to the work of Lincoln¹². Without going into detail, we shall briefly outline three cases from our service.

First, a case of cervical adenitis at the age of two, followed during the next two years in turn by a tuberculous effusion into the knee joint and quadriceps bursa, and pulmonary involvement of the upper half of the right lung, with hemorrhage. All lesions are now clearing.

Second, a case with scattered, fine mottling through the lungs and enlarged hilus glands, scattered fluctuant subcutaneous abscesses containing tubercle bacilli, distention, fluid wave and indefinite masses in the abdomen. Periodic partial intestinal obstruction occurred, but the lung lesion remained unchanged at the end of nine months.

Third, a case under observation for over two years, with marked

calcification in the upper right lung, entering with a tuberculous lesion of the right hip followed by tuberculosis of the left elbow, dorsal spine and lumbar spine. In all the above cases, a source of infection was found in the family.

These brief summaries show how pleoform may be the manifestations in children. The picture is quite different from that of acute miliary tuberculosis and deserves emphasis as its essential haematogenous nature is often at first not appreciated.

GROUP IV OLD PULMONARY TUBERCULOSIS WITH TERMINAL HAEMATOGENOUS SPREAD

Of the forty-six cases here reviewed, eighteen were judged to fall into this group. This termination of pulmonary tuberculosis is well enough known. It is quite different from the picture where blood borne disease is early recognizable. All but two of these cases are dead, eight were autopsied. Of the autopsied cases, in addition to a complex lung picture and widely scattered lesions elsewhere, there were major lesions in the genito-urinary tract in six cases, adrenal tuberculosis in one case and a terminal acute miliary disease alone in one case. In the deceased unautopsied, and the living cases, the major lesions outside the lungs were as follows: Genito-urinary tract, 4; Meninges, 4; Bone, 1; Peritoneum, 1. One case had skin tuberculides. From these data, the story can be reconstructed thus: With old pulmonary disease, severe extrapulmonary lesions are most apt to occur in the genito-urinary tract or meninges and to less extent in bone, peritoneum or adrenal gland, terminating in a final acute miliary tuberculosis.

As the haematogenous element in this group is decidedly secondary to chronic pulmonary tuberculosis, these cases are not especially interesting for our purposes and will not be further discussed.

Cases without extrapulmonary lesions

GROUP I HEALED MILIARY TUBERCULOSIS

CASE 7—Male, laborer, age thirty eight. This man was discharged from the Navy in 1918, with a diagnosis of pulmonary tuberculosis. He remained in the hospital only three months, was sent home and remained well thereafter. He entered the Albany Hospital for repair for an inguinal hernia in 1934. He was a poorly developed individual and had some cough and thin mucoid sputum in which no tubercle bacilli could be found. A few rales were heard in the upper right chest. The chest roentgenogram showed discrete, shotty and apparently

calcified nodules scattered diffusely throughout both lungs. On close questioning, he said that he had been subject to frequent colds and had a continued slight cough, occasionally expectorating a very small amount of bloody sputum. Some few months later, his condition was unchanged.

This is apparently a case of healed, miliary tuberculosis. Bronchogenic tuberculosis does not heal leaving these widely disseminated nodular calcifications.

GROUP II CASES WITH HAEMATOGENOUS LUNG CHARACTERISTICS BUT NO EXTRAPULMONARY LESIONS

CASE 8—Housewife, age forty (figs 5 and 6). This patient was first seen in April, 1931, at which time she complained of indigestion and slight dyspnea. Although she was a very frail looking individual she gave no history of acute illness and had managed her own home.

Physical examination revealed no abnormal lung signs, but the roentgenogram showed stringy shadows throughout the chest. There was no evidence of nodular structure in these shadows. The sputum was negative and no diagnosis other than pulmonary fibrosis was made. In August of that year, cough and expectoration of a mucoid sputum began and continued through the following winter. She became weaker and more dyspneic and entered the Sanatorium in 1934. The left chest was filled with coarse and medium coarse rales. The roentgenogram now showed a great increase of stringy shadows through both lungs and some overlapping ring shadows, suggesting cavities. She went home, but later returned again and died of respiratory embarrassment and circulatory failure in 1935, four years after she was first seen.

During the last year, twenty five sputum specimens and four guinea pig inoculations were negative. Studies for yeast, moulds and other organisms in the sputum were inconclusive. The white blood count remained rather high. A typical count on April 12, 1935, was, white blood cells, 14,900, polymorphonuclear leukocytes, 45 per cent, eosinophils, 5.5 per cent, lymphocytes, 42 per cent, mononuclears, 7.5 per cent. The persistently high lymphocyte count suggested a markedly organizing type of lesion, as, in fact, it was. It was only after death that tuberculosis developed in a guinea pig inoculated with her sputum. No postmortem was granted.

This case represents (if we accept the tuberculous etiology) the ultimate in the diffuse fibrotic form of haematogenous tuberculosis. It is highly probable that many cases of lung fibrosis of obscure etiology are of this type and escape the diagnosis of tuberculosis.

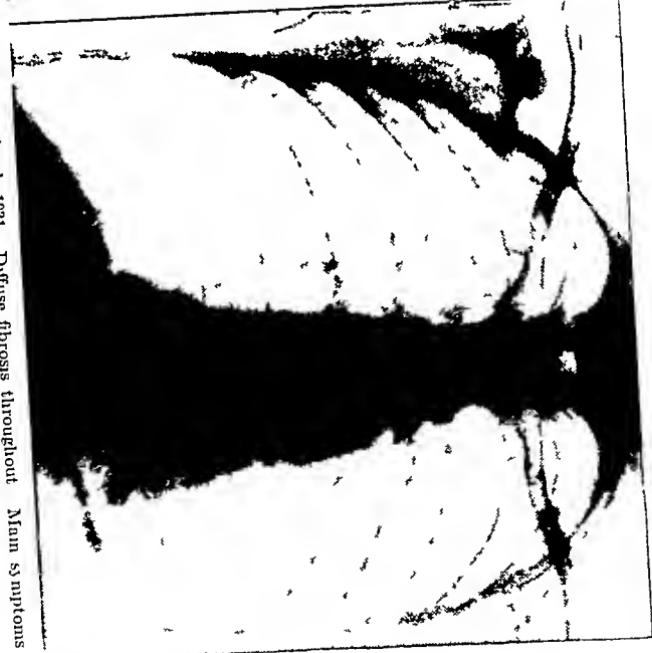
CASE 9—Male, painter and paperhanger, age forty. This patient first entered the Sanatorium in 1930 complaining of recent fatigue and loss of weight. Physical examination revealed rales in both chests, down to the second rib and the roentgenogram showed moderately coarse mottling scattered throughout both lungs. No tubercle bacilli were found in the sputum. He improved markedly and left at the end of two months.

FIG 4



Case 6. Scattered cleftification fibrosis and some moderately fine nodular mottling throughout. Fibrosis more marked and ring shadows suggesting cavities in upper left. Tuberculous epididymitis. Entire absence of all respiratory symptoms

FIG 5



Case 8 n. April 1931. Diffuse fibrosis throughout. Main symptoms dyspnoea and weakness

FIG. 6



FIG. 7



Case 8 (b) August 1934 Great increase of fibrosis three and one half years later Little cough or expectoration Died May 1936 Sputum positive only a month before death

Case 7 Healed miliary tuberculosis

Three years later, he returned complaining of the same symptoms (fatigue and loss of weight), and some bloody sputum, chills and fever. On this admission, the roentgenogram showed the same pattern of lung lesion widely spread through the lungs. It differed, however, in that now there were stringier and more fibrotic lesions lying around and between somewhat more hazily outlined and softer looking nodular shadows. In six months, these nodular lesions became quite discrete and firm looking and a marked fibrosis dominated the picture. Extensive sputum studies were made. The flora was a varied one but no tubercle bacilli or pathological fungi were found. In spite of this fact it was felt that the lesion was tuberculous. Clinically he improved greatly and now, although not robust, he remains well.

In such cases, it may be that the changes noted are not due so much to fresh dissemination of tubercle bacilli as to an altered allergic state causing exudation around old foci which quite rapidly subsides, an intrapulmonary tuberculin reaction, so to speak. The factors of allergy and immunity, dosage of bacilli and virulence of organism all play a part in the way disease behaves. Such factors can only be suggested in this paper.

GROUP III REPEATED PLEURISIES

That involvement of serous membranes (pleura, meninges and peritoneum) is more frequent in haematogenous tuberculosis than in other forms, has been recognized by many authors.¹³ In fact, it is believed by some that pleurisy with effusion is usually caused by haematogenous infection. As the seeding of tubercles is more peripheral than in bronchogenic tuberculosis, this seems reasonable. Especially has this association been emphasized in cases with repeated and bilateral pleurisies. Four such cases occurred in this series. They showed little disease in the lung and such lung lesions as appeared became obvious only later in the disease. Weeks or months intervened between the attacks of pleurisy.

CASE 10.—Female, age twenty three, housewife. This patient was first seen in the Out Patient Department on May 17, 1933, complaining of pain in the right side of the neck and lower right chest. A few rales were heard at the right base. A diagnosis of diaphragmatic pleurisy was made and, after a short stay, she went home. One year later she returned, quite ill, with a small effusion at the opposite, or left base. Freidlander's bacillus and pneumococcus Type IV were found in the sputum but smears were negative for tubercle bacilli. The roentgenogram revealed nothing but the effusion. Tuberculous pleurisy was diagnosed and sanatorium care advised. This was refused. She was readmitted a month later with an effusion at the right base (the site of the pleurisy of the year before). This was aspirated and tubercle bacilli recovered from the fluid. She then entered

the Albany Hospital Sanatorium. A subcutaneous abscess appeared in the region of the aspiration and sterile pus was aspirated ten weeks later. A large ulcer, with undermined edges formed, which finally healed completely.

During this residence, the patient developed considerable tenderness through the abdomen, distention appeared and the umbilicus protruded. Although no aspiration was done, a diagnosis of tuberculous effusion into the peritoneal cavity was made. Rales also appeared at both lung bases and still persist. She recovered and is now clinically entirely well, without pulmonary or abdominal symptoms.

The roentgenogram on July, 1934, showed a scattered, fine hazy mottling at both bases. By July, 1935, this had definitely increased. By September, 1936, it had cleared greatly and little abnormal remained, except a few small nodules scattered through both lung bases.

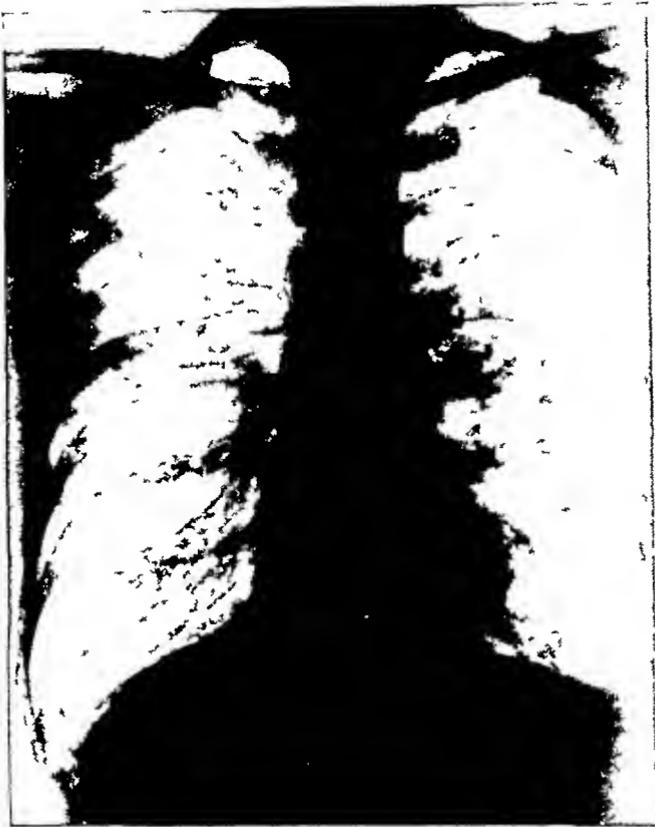
SUMMARY AND DISCUSSION

Tuberculosis, as seen at autopsy, is rarely a sharply localized disease. In almost all cases the distribution is very wide, whether or not extrapulmonary lesions cause gross disease. A study of pulmonary tuberculosis at autopsy or during life, in which extrapulmonary lesions are prominent (and thus demonstrate a large haematogenous element), reveals certain characteristics which we can trace in other cases where the extrapulmonary lesions are not obvious. In general, the characteristics of haematogenous pulmonary tuberculosis are the wide dissemination and uniform character of the lesions, the paucity of respiratory symptoms and physical signs, and the mild course of the disease.

To this general picture there are many exceptions. At the one extreme there are the acute or subacute miliary forms in which overwhelming infection soon causes death. At the other extreme are forms healing by absorption, fibrosis or calcification, with slight clinical evidence or history of disease. Between these extremes there are infinite gradations. Lesions may vary greatly in size, they may be few or many, dissemination may be at one episode or by repeated crops through long periods of time, so that many stages of lesions are present at one time. Lesions may eventually coalesce, forming dense patches or may be complicated by secondary bronchogenic spread.

The possibility of blood borne dissemination emphasizes the advisability of elimination of obvious and easily approached lesions, as in the epididymis and also the importance of minimizing trauma during the removal of such foci.

FIG 8



Case 9 Scattered nodular and stringy hadows throughout Recurring clinical symptoms observed for three years Clinical recovery



On the other hand, properly understood, the benign nature of some cases often justifies giving a better prognosis than would otherwise be possible. Especially is this true as regards some cavities. They may be watched for a longer time before mechanical methods of closure are employed.

By a study of the simpler forms in which there can be little disagreement, we learn to recognize more obscure evidences of blood borne disease in the more chronic and complicated forms. An appreciation of this may affect in some ways our practical handling of these cases. The silent nature of these chronic forms, if properly understood, re-emphasizes the importance of adequate rest for complete encapsulation of lesions, especially where extrapulmonary lesions have once been manifested. It also makes us cautious, in certain instances, in using the mechanical adjuncts to treatment, especially the irreversible ones such as thoracoplasty. What often is thought to be a fresh bronchogenic spread may often be the reawakening of a little evident haematogenous lesion on the good side because of allergic changes.

The great advances made in surgery of the chest has tended to make us mechanically minded and to approach pulmonary tuberculosis as a local disease to be cured by local chest procedures. The more emphasis we place on the various haematogenous manifestations of disease, the more shall we look upon tuberculosis as a generalized disease and the better we shall be able to select cases for such treatment and regulate such procedures.

Our ideas of the epidemiology will be profoundly influenced by our knowledge of this form of disease. If we believe that later and varied lesions in tuberculosis are due to exogenous reinfection, we may well question, at least from the patient's viewpoint, the advisability of concentrating and treating large numbers of people with open disease in sanatoriums or similar institutions. Without minimizing the infectious nature of tuberculosis, it is safe to say that the more we emphasize the endogenous origin of reinfection, the more importance we shall place on haematogenous dissemination as an explanation of developments in the disease.

In conclusion, we may say that further knowledge of haematogenous manifestations will influence considerably our thought on the

epidemiology, the diagnosis, prognosis and the treatment of pulmonary tuberculosis

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Syphilis

ORAL SYPHILIS*

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EVERY well trained physician makes it a rule to examine the mouth as part of his routine investigation. Truly it is the most contaminated cavity in the body, 60 per cent of all infectious diseases are said to enter the system through the mouth. If a pathological lesion is present he may have difficulty in diagnosing the condition. A general inspection of the entire skin may determine whether the disease is an oral manifestation of a generalized disease or exanthem. The clinical picture he expects to find may be clouded by certain conditions present which reduce the characteristic features to a uniformity of appearance. Thus, friction, moisture, trauma, previous local and general treatment, secondary infection and constitutional factors may modify the clinical aspect of the case. Small wonder then that the physician often admits "All mouth lesions look alike to me."

The patient with a mouth lesion is concerned to a greater extent than if he had a similar cutaneous disorder. Especially in women cancer-phobia will be found and the patient's fears must be relieved. A Wassermann and Kahn test should be performed on every case to rule out that well-known capricious disease—syphilis. No diagnosis should be attempted without a complete history, a complete physical examination including the entire skin and laboratory tests if indicated.

Oral syphilis is not easily diagnosed. Its manifestations may be so slight in the beginning as to be missed in the routine examination. In order to determine its frequency an analysis was made of 374 cases of oral disease seen in the dermatological clinic at Firmin Desloge Hospital during 1935. The results are as follows:

* From the Department of Dermatology and Syphilology, St Louis University

| | |
|-----------------------------|-----|
| Herpes simplex | 112 |
| Bismuth stomatitis | 68 |
| Oral syphilis | 63 |
| Vincent's disease | 35 |
| Drug eruptions | 26 |
| Leucoplakia | 21 |
| Electro-galvanic stomatitis | 15 |
| Miscellaneous | 34 |
| | — |
| | 374 |

The frequency of oral syphilis of all types in the series as tabulated above was 16.8 per cent. This percentage is higher than that found in general practice since the diagnosis and treatment of syphilis is concentrated in the dermatological clinic at Firmin Desloge Hospital.

It is of course self-evident that a positive serological test in a case of mouth disease does not necessarily label it syphilitic. There were three cases of pernicious anemia in our series with glossitis and strongly positive Wassermann tests which required careful analysis. Late gummatous lesions of the tongue with negative serological tests are also frequent.

A survey made in 1935 showed that the incidence of syphilis at Firmin Desloge Hospital was 8.5 per cent. In order to avoid hasty diagnosis, every mouth case was studied on its merits clinically, with laboratory confirmation only as a last result. In eight (12 per cent) of the cases of oral syphilis there were typical genital lesions which helped to establish the diagnosis. A good rule to follow is "where there is a mouth condition, don't overlook the genitals."

Syphilitic sore throat may vary from a mild laryngitis to severe involvement with hoarseness. In every case in which a culture is indicated, a Wassermann test should be taken at the same time to avoid a common error in diagnosis.

The types of oral syphilis as seen in this survey were as follows:

| Type | Positive Serology | | | |
|-------------------|-------------------|----------|-------|----------|
| | Cases | Per Cent | Cases | Per Cent |
| Primary | 11 | 17% | 8 | 72% |
| Early (secondary) | 32 | 50% | 32 | 100% |
| Late | 12 | 19% | 7 | 58% |
| Congenital | 8 | 12% | 7 | 87% |

The high percentage of positive Wassermanns in the primary group is not unusual since patients with extragenital lesions usually appear for treatment much later than those with genital sores¹. Mucous patches were the commonest lesions (87 per cent) with 100 per cent positive Wassermanns compared to 99 per cent found in the group of 2269 patients with secondary syphilis studied by the Co-operative Clinical Group. One-half of the syphilitic mouth lesions were those of the secondary stage. The Clinical Co-operative Group² reported that 36.3 per cent of their patients with secondary syphilis had lesions in mouth and throat.

Primary lesions accounted for 17 per cent of the total number of cases. The lip as the most frequent site of this type of lesion is borne out by the figures (72 per cent). Late lesions may often be identified with negative serological tests which may influence the observer. In our series only 58 per cent of the cases had positive Wassermann tests. The tongue was affected in 59 per cent of the cases and the palate in 41 per cent. Interstitial keratitis was a common finding in those patients with the congenital variety (94 per cent).

In the primary type there were eleven chancre, two of the lesions occurring on the tongue, one on the right tonsil and eight on the lower lip. Of the thirty-two early lesions twenty-eight were mucous patches and four were the erosive or split-papule type that affect the commissures.

The commonest type of late lesion was interstitial glossitis with five cases. Smooth atrophy of the tongue, an important lesion, often a solitary sign, totaled two cases. There were two gummatous of the soft palate and three perforations of the palate.

Of the congenital variety there were seven cases of Hutchinson's teeth and one case of rhagades or circumoral scarring. Two of this group had latent neurosyphilis.

The physician as well as the dentist should be impressed with the frequency of the oral manifestations of syphilis. The latter should not attempt a diagnosis but should be able to detect a pathological condition and send the patient to a competent physician.

PRIMARY ORAL LESIONS

The lip chancre comprises about one-fourth of all extragenital lesions, due to the popularity of mouth to mouth contacts. An early

sign is the enlargement of the submaxillary glands. The lesion may straddle the lip, erusted on the cutaneous portion and erosive on the mucous membrane portion (pouting type). The erosive and ulcerated types are the commonest but papular, hypertrophic, phagadenic and commissured (fissured) forms may occur. Herpes can be distinguished by the fact that it consists of a superficial group of vesicles surrounded by an inflammatory area and by the absence of induration. There is always a history of acute onset or previous attacks. A furuncle on the lip may sometimes simulate a primary infection. However the history of acute onset, the presence of pain, slight adenopathy, absence of crusting and laboratory evidence of leukocytosis will help to establish the correct diagnosis. Carcinoma bleeds easily, there is a characteristic peau d'orange border and the absence of signs of acute inflammation in the untreated case. There may be a co-existing leukoplakia which is an important point. Of course the dark-field is negative in carcinoma, it may be also negative in the case of a chancre which received local treatment. In gumma of the lip there is no satellite bubo. Chancroid of the lip is very rare and usually associated with genital lesions. Tuberculous ulcers of the lip are usually painful, tuberculosis will be found elsewhere and smears are positive for tubercle bacilli.

Many cases of chancre of the tonsil escape detection. It is surprising to know that they are next to the lips in frequency. They usually occur in women, the right tonsil being more frequently involved than the left. It is unusual to see two cases that are alike. The following types may be distinguished (1) erosive, (2) ulcerative, (3) quinsy-like, (4) diphtheroid and (5) gangrenous. Constitutional symptoms such as fever, chills, headache, malaise and joint pains may occur and are probably due to mixed infection. The characteristic symptoms which are persistent with gradual onset are not influenced by local measures and consist of sore throat, slight pain and submaxillary tenderness due to lymph gland enlargement. Occasionally there is a sensation of burning pain or discomfort in the ears or partial deafness. The tonsils are enlarged, deep red, and the fossae are injected. The induration may be difficult to appreciate unless the gloved finger is used to palpate the lesion. Some of the lesions are covered with an adherent grayish membrane, which may

be mistaken for diphtheria, Vincent's disease or streptococcus sore throat

There are four types of extragenital primary lesions of the tongue (1) ulcerative or excavated, (2) smooth or sclerotic, (3) fissured (usually occurs in the folds of the tongue) and (4) phagadenic, which is rare. The submaxillary and deep cervical glands usually become enlarged early. The lesions may be solitary or multiple. They are very much indurated at the base and edges. About 90 per cent of the lesions occur on the dorsal surface near the tip of the tongue. The source of infection may be from kissing, pipettes, infected musical instruments, pipes or through sexual contacts. There is little or no pain, no interference with function, no deformity. The duration of the untreated lesion is from five to twelve weeks. There are no subsequent scars although leukoplakia may follow, especially if caustics were used before the correct diagnosis was made.

The importance of the gum chancre from the standpoint of diagnosis is self-evident. Fortunately there lesions are rare with an incidence of 5 per cent. They are often so uncharacteristic in appearance that they are missed even by experienced syphilologists. Friction and the modifying effect of the bacterial flora of the mouth may be responsible for this fact. The common type is a slight erosion with a "muscle" color and an oval or orbicular shape. The lesion is rarely larger than the size of the nail of the little finger, the upper border being crescentic and convex and the lower border having a concave border extending over two or three teeth. There may be some inflammatory edema of the gum. The floor of the erosion is often bright red in color. In rare cases it may be covered with a dirty gray or diphtheroid membrane. The ulcerative type which may be purulent or sanguineous is more angry looking. Its color has been described as "rouge carminee" by French writers. Papular gum lesions are extremely rare.

The majority of gum chancres occur anteriorly on the upper gums (twelve times more common than on the lower gum) in the vicinity of the incisor or canine teeth. This is especially true if the infection is venereal. If the infection is caused by contaminated dental forceps or instruments, the traumatized tissue will be the site of the lesion.

There may be some pain during mastication but the majority of

gum chancres are more or less benign in appearance with symptoms which dispel suspicion

The submaxillary and preauricular lymph gland groups are usually involved. Occasionally there is slight fever. The involved glands may be painless but are often large and sometimes inflammatory.

About half the cases are acquired through unnatural venereal contacts. Glass blowing, dental instruments, infected pencils, tooth brushes and tooth picks, and kissing have been factors in some cases. The rôle of dental trauma is not as important as some authors would indicate. If infection in post-extraction cases occurs, the traumatized tissues make a splendid portal of entry.

The differential diagnosis concerns alveoloperiostitis, ulcerative stomatitis, epulis, aphthous stomatitis and gingivitis. A dark-field examination and Kahn test are indicated on all suspicious lesions before local treatment is applied.

SECONDARY ERUPTIONS OF SYPHILIS

The most common, most infectious and most dangerous lesion of syphilis is the mucous patch. It is not an ulceration, but an erosion. It has been aptly described as having the appearance of a silver nitrate eschar. The favorite locations are the mucous membrane of the upper and lower lip just back of the vermillion border, the anterior pillars of the tonsils, the buccal surfaces where the teeth meet, and, less frequently, on the soft palate, tongue and tonsil. The lesions, mildly inflammatory, are sharply marked, oval and round and covered with a gray translucent membrane. They are not very painful to the touch. While evanescent as a rule and visible to the naked eye for a few days, they may be persistent, often lasting as long as three weeks when untreated. The treponemata are demonstrated with difficulty by the dark-field illuminator. Mucous patches must be differentiated from herpes (canker sores), Vincent's angina, geographic tongue and crythema multiforme.

LATE ORAL SYPHILIS

Gummata of the tongue are always late manifestations. Since they are due to an underlying endarteritis of the deeper tissues the lesions evolute gradually. Trauma often initiates their growth. The center of the tongue is the site of predilection as opposed to car-

cinoma which almost invariably attacks the edge of the organ and by extension, the floor of the mouth. The borders of the gumma are soft, although there may be a raised indurated area surrounding it. Carcinoma is hard and painful, grayish in appearance and often interferes with speech. Invasion of the floor of the mouth which is associated with marked fetor oris, is soon followed by hard, shotty glands in the submental region and in front of the angle of the jaw. The gumma is not accompanied by adenopathy. In any case in which the diagnosis is doubtful, a biopsy should be performed and the sections studied by an experienced pathologist.

GUMMA OF HARD PALATE

Of the bony structures of the mouth the hard palate is most frequently involved. The palate is first undermined by the syphilitic process, usually a submuco-periosteal gumma, which makes its visible appearance only when the mucoperiosteum breaks down secondarily. The buccal surface of the palate is affected first but prompt anti-syphilitic treatment will often prevent a perforation. These lesions are usually situated in the center of the hard palate and often follow trauma. It is not uncommon for destruction of the nasal bones to occur at the same time. Perforations frequently occur in the soft palate, occasionally the uvula is amputated by a syphilitic process. Often the characteristic voice of the patient with its nasal quality leads the diagnostician to examine the nasal and palate bones.

LEUKOPLAKIA AND SYPHILIS

Leukoplakia is primarily a defense mechanism, the membrane protecting itself against irritation by keratinization of the mucosa and sclerosis of the derma. It is usually limited to the buccal membranes where the teeth meet, forming an irregular, mosaic-like, whitish, slightly indurated thickened line. This condition is especially to be found in individuals with ill-fitting plates or jagged teeth.

While leukoplakia almost invariably occurs in chronic smokers and tobacco-chewers, yet it does occur in non-tobacco users. The rôle of syphilis as an etiological factor in this condition is not definite but not more than 5 per cent of the buccal cases can actually be due to the infection. McCarthy³ and others point out that leukoplakia limited to the tongue is often caused by syphilis especially if there is a history of previous specific involvement. French writers⁴ who con-

sider atrophic glossitis of syphilitic origin as a form of leukoplakia are less open to doubt and give figures varying from 20 to 95 per cent. Consequently, syphilis plus irritation is the greatest factor in the production of this condition, since the infection lowers the resistance of the mucous membrane and increases its irritability.

There are three types, (1) the smooth or common type, (2) the raised plaque type and (3) the verrucous type which often develops malignant changes. The common type, even though it develops upon a syphilitic basis, responds slowly to any type of antiluetic treatment. The lesion may be only a millimeter in size, covered with an opalescent, translucent membrane and limited to the lower lip, or it may be a thick, curd-like area involving the entire tongue, inner cheeks, lower lip or gums. When the lesion is limited in size, characteristic cross-cross lines are present which divide the area into small squares and triangles, but if the lesion is extensive, these markings are lost and certain areas, especially the tip and base of the tongue may become locally circumscribed and much thickened. Under these conditions, the lesion may take on a yellowish color and develop fissures in the center or at the commissure of the mouth. If the patient is a tobacco-chewer, a grayish or brownish verrucous surface often appears where the chew is held.

These local hypertrophies are in danger of undergoing malignant degeneration and whenever seen should be treated with radium, excision, or cautery. In an extensive leukoplakic involvement, especially of the gums, tooth extraction is a dangerous procedure since leukoplakia may rapidly spread to toothless sockets and often end in malignancy. The Wassermann reaction is negative in the majority of these cases.

Of the twenty-one cases of leukoplakia in this series, one case occurred in a woman, the other twenty were in males. Five of the cases had positive Wassermann tests (20 per cent) but none improved under syphilitic therapy alone. With attention directed to dental and mouth hygiene none of the cases required surgical intervention.

CANCER OF THE MOUTH AND SYPHILIS

All authorities agree that the presence of syphilis increases the degree of malignancy of oral carcinomata by destroying the cellular

balance of the tissues Prinz and Greenbaum⁵ point out that cancerous degeneration, usually of the prickle-cell type is most commonly observed in cases in which syphilis constitutes a complicating factor Eller⁶ states that 60 per cent of all carcinomata of the tongue develops on syphilitic soil It is also his opinion that 25 per cent of all other buccal malignancies occur upon a syphilitic base Carcinoma and syphilis may certainly co-exist, both may be active in the same lesion Sections may prove that the syphilis is the dominant factor or as is usually the case, it may be only in a latent phase Regardless of the serological evidence however, every suspicious growth in the mouth should be subjected to an immediate biopsy to settle the diagnosis

The writer is not in accord with those who suggest therapeutic tests with antiluetic drugs in order to determine the nature of a tumor of the mouth A recent statement, is especially vicious, viz "if lues is suspected treat the patient with antiluetic therapy for three weeks only and then if the lesion is not healed, carcinoma should be suspected and a biopsy obtained" Not only is precious time lost by this procedure but there is reason to believe that arsenic has a stimulating effect on malignant tissues The growth may shrink the first few weeks due to the non-specific effect of the arsenical drug and lull the physician's suspicions concerning the true nature of the lesion he is treating The non-specific effect of arsphenamine in inoperable sarcomata of the mouth in non-syphilitics has been disappointing in my hands

THE DENTAL ABNORMALITIES OF CONGENITAL SYPHILIS

Examination of the teeth provides the observer with important facts in the recognition of congenital syphilis Care must be employed not to rate all dental dystrophies as syphilitic since various febrile and nutritional conditions often cause dental defects

The first point to remember is that only the second dentition teeth show changes distinctive and pathognomonic of syphilis The teeth of the first dentition may be delayed or subject to early decay, changes which occur in many serious constitutional diseases The only positive diagnostic sign is the Hutchinsonian incisor while the suggestive signs are the mulberry molar, microdontia, spacing or crowding of the teeth and malocclusion One or more of these suggestive dental signs

in a patient with the facies of congenital syphilis (frontal bosses, wide spacing of the eyes, circumoral scarring and saddle nose) simplify the diagnosis.

The upper central and occasionally the lateral incisors which undergo development and ossification during late uterine and early infant life bear the brunt of the syphilitic dystrophy. Syphilis suppresses the middle denticle which forms the central portion of the tooth. At the same time the lateral denticles continue to grow and produce the bulging sides and barrel-shape of the characteristic syphilitic incisor. The cutting edge of the tooth lacking the middle denticle develops the characteristic notch of the typical Hutchinsonian tooth. When notching is absent, the shape of the tooth still may be diagnostic. To an incisor with a narrowed cutting edge, with separation, the term "screw-driver" tooth is applied.

Another group of teeth that show distinct changes are the first or six-year molars which develop defective cusps described as "mulberry molars". The four cusps become dwarfed, deficient in enamel and decay early. Loss of the cusps produce a smoothness of the grinding surface with pitting. Some investigators have found the "mulberry molar" a more frequent and suggestive sign than the "Hutchinsonian tooth" but the tendency to error is too great to stress the condition. It is however a valuable sign to the expert when typical and may be the only positive dental abnormality present in a patient otherwise negative but who has positive serological tests and a suspicious family history.

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NEUROLOGICAL CLINIC

Meningo-Vascular Syphilis of the Cord Brown-Sequard Syndrome*

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THIS case presents certain interesting points of diagnosis and a classical anatomical syndrome which is seldom so clearly demonstrated. Will you be good enough to give a summary of the history?

STUDENT The patient (C A S, unit 19088) is a married man, sixty-two years of age. At present he is working as a farm manager, the job requiring clerical work alone. Both his mother and father died of carcinoma of the stomach.

At the age of eighteen the patient fell from a horse and injured his back. He had transient blindness for two or three hours. At the age of thirty-seven he fell off a scaffold and landed on his heels. He was unconscious for about fifteen minutes. There is the story of a primary sore at the age of twenty-two. He has been married for thirty years. His wife and two children are living and well. A review of the systems is negative.

At the age of forty-two the patient had a sudden attack of pain involving the whole upper part of the body lasting two weeks. At the end of this period he suddenly became unconscious and fell to the floor. He did not injure himself. The unconsciousness persisted for four hours. He consulted a doctor. At that time loss of pain sensitivity was first demonstrated. We do not know of its distribution. The Wassermann reaction was found to be positive in the blood. He received treatment for a month which consisted of injections of arsphenamine once a week and mercury rubs. The treatment was continued at irregular intervals for two years.

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At fifty-two the patient noticed that the fourth and fifth fingers of the right hand first felt numb. The next year he noticed some weakness and atrophy of the muscles of the right hand and the extensor surface of the right arm. He had another course of six treatments of salvarsan and mercury during this year and also a course the following year. The tonsils and five teeth were removed in an attempt to stay the symptoms.

During the early part of 1928 when the patient was fifty-four, the atrophy seemed to be progressing. There was some weakness of the left hand. He noticed that on walking down stairs he threw his feet out further than he should. For a year he had found that he was unsteady on his feet, particularly with the eyes closed. He observed some loss of pain-temperature sensation, particularly over the right arm. Ever since the beginning of the illness there has been quivering of the muscles which he was unable to control.

In 1928 the patient came to this hospital. On neurological examination the findings were very similar to those observed now, though slightly less severe. The Wassermann reaction was negative in the blood. Examination of the spinal fluid revealed a two plus Pandy test. The Wassermann reaction was 2+ at a dilution with 0.8 cc of serum. The mastic curve was 3332000000. A roentgenogram of the spine showed no abnormality.

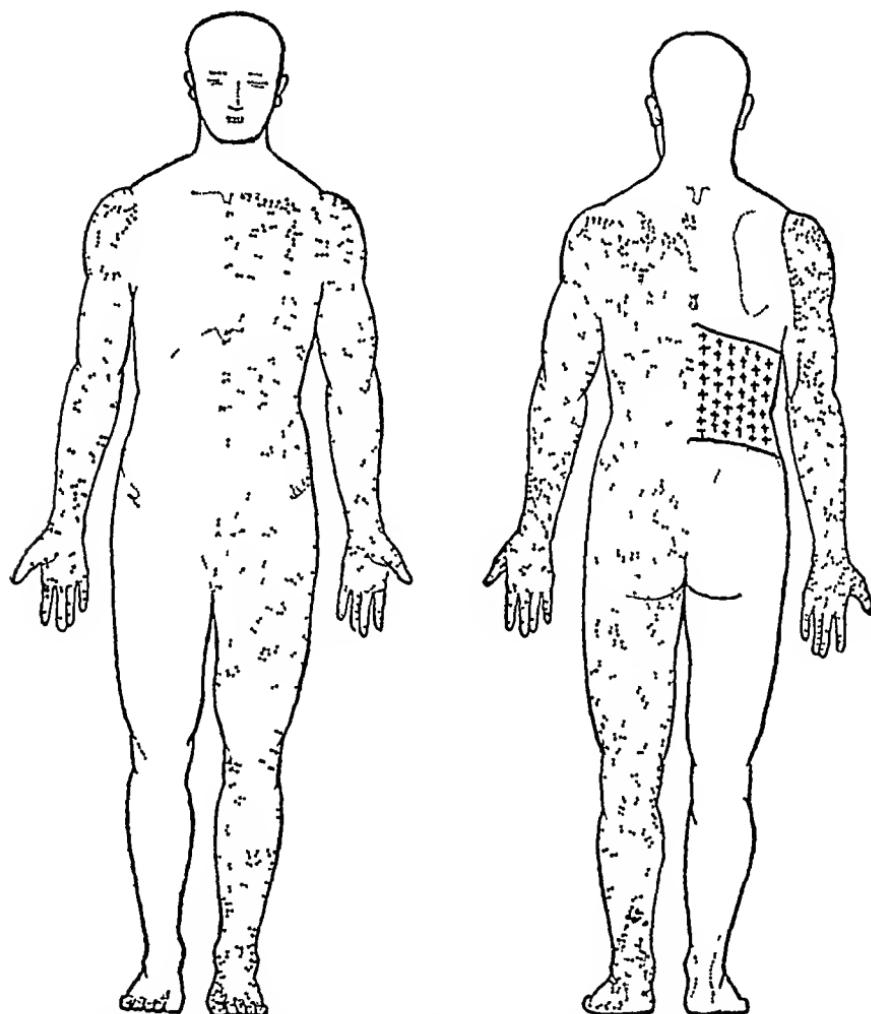
A Queckenstedt test revealed a complete block of the subarachnoid space. Lipiodol when injected did not pass the block which appeared as an abrupt level at the fifth cervical vertebra. A laminectomy was done, and the patient states that a tumor was removed. The report of the findings will be given in detail later.

Following discharge from the hospital eight years ago his general health has gradually improved. The hand and arm on the right side showed no return of function, and indeed became gradually weaker and more atrophic. There has been severe constipation for fifteen years. Libido and potency have been lost for an equal time. The patient has noticed urgency and frequency of micturition for eight years. There is nocturia one or two times a night. Two years ago he noticed that the left hand and right leg were weaker. Now he has a noticeable limp. He has burned his right hand without knowing it. During the last six months the patient has felt increased pain and a hypersensitivity to heat and cold over the back on the right side.

Because of this increased disability he has returned for another examination. The spinal fluid Wassermann reaction has been found persistently negative for the past fifteen years.

The left triceps jerk is absent. The other deep reflexes are sluggish in both arms. There is no Hoffmann reflex. The abdominal and cremasteric reflexes are sluggish on the right. The right knee jerk is hyperactive, the left is sluggish. The ankle jerk is elicited on the right but it cannot be demonstrated on the left side. The Babinski reflexes are positive bilaterally. There is no clonus.

FIG. 1



The dotted areas upon the figure indicate the areas of loss of pain-temperature sensation. The area upon the back indicated with plus marks shows the distribution of the hyperesthesia.

In the right arm there is loss of pain-temperature sensation over a segmental area from the fifth cervical to first thoracic areas inclusive.

On the left side there is a loss of pain and temperature over the extremities and trunk extending as high as the upper border of the fifth cervical segment. Vibratory and sense of passive movement are lost in the right leg. Tactile sensation is everywhere grossly normal. There is astereognosis in the right hand.

Over the right side of the back from the eighth thoracic to twelfth thoracic segments there is hyperesthesia to pain, heat and cold. The patient has been subjectively aware of this hyperesthesia. Palpation of the deep back muscles in this region is painful.

There is an enophthalmos on the right. The palpebral fissure is narrower on that side and the pupil is smaller. What do these findings suggest to you?

STUDENT A Horner's Syndrome on the right.

What relation has this syndrome to the other neurological findings?

STUDENT It suggests an injury of the upper thoracic portion of the cord on the right side.

Will you draw a diagram demonstrating the areas on the body which show loss of pain-temperature sensation?

(See chart in figure one)

What do we call this type of injury to the spinal cord?

STUDENT The Brown-Sequard Syndrome.

What does this syndrome imply anatomically?

STUDENT A hemisection of the spinal cord.

What findings suggest this type of lesion?

STUDENT Below the level of the lesion there is loss of pain-temperature on the opposite side of the body. At the level of the injury there is loss of pain-temperature sensation on the same side of the body. There is paralysis of the extremities on the side of the lesion and a positive Babinski reflex on that side. Vibration and sense of passive movement is lost on this side also.

How do you explain the loss of pain-temperature sensation at the level of the lesion on the affected side of the cord?

STUDENT The injury occupies a considerable longitudinal extent and therefore all afferent fibres, including those carrying pain and thermal sensation, will be injured throughout this region.

What is the longitudinal extent of the lesion in this case?

STUDENT It extends from the fourth cervical segment to the first thoracic segment.

Can all the physical findings be explained on a lesion of this extent?

STUDENT No The atrophy of the trapezius and sternomastoid muscles on the right suggests some injury to the third cervical segment

Are all the findings those of the Brown-Sequard syndrome?

STUDENT No The atrophy and fibrillations of both hands and forearms are not characteristic and imply a more extensive lesion. Nor is the bilateral Babinski response explainable on a hemisection alone

What other type of lesion do all these findings suggest?

STUDENT Syringomyelia

ANATOMICAL DISCUSSION

The Brown-Sequard Syndrome —The Brown-Sequard Syndrome is an anatomical concept which is seldom perfectly realized. It would be next to impossible to cut through just half of the spinal cord experimentally. Moreover it is difficult to study sensory loss in an adequate way in experimental animals. Similarly in clinical neurology the syndrome is rarely complete without extraneous findings. The present case is perhaps as perfect an example as could be expected.

I intend, therefore, to take time to consider with you in some detail the picture of the Brown-Sequard syndrome. Inasmuch as Brown-Sequard himself was such a brilliant investigator and colorful personality, I propose first to give a short sketch of his life and bring to your attention some of his more famous publications.

Brown-Sequard, was born in Mauritius in 1817, the son of an American father and a French mother. After a scanty preliminary education, he received his doctor's degree in Paris in 1864. His thesis was concerned with reflex action of the spinal cord. Early in his career he was made professor of medicine and medical jurisprudence at the Virginia medical college. Not finding this position congenial, he returned to Paris and opened a private physiological laboratory where he taught pupils. In 1856 he established at his own expense the *Journal de Physiologie*.

Following a lecture on the anatomy and physiology of the nervous system at the Royal College of Surgeons in London, he was made a member of the Royal Society. When the National Hospital on Queen

Square was opened he was asked to be one of its physicians. In 1863 he was made professor of physiology and pathology of the nervous system at Harvard. Later he returned to France to hold a similar chair in the faculty of medicine in Paris. Following the death of Claude Bernard in 1878, he filled the chair in experimental medicine of the college of France.

Among his scientific contributions, the following may be mentioned. He traced sympathetic nerve fibers into the spinal cord. Experimental epilepsy was produced in guinea-pigs. With Claude Bernard he demonstrated vasomotor nerves. He established on a firm scientific basis much of the knowledge of disease of the nervous system. He was also with Claude Bernard the principle founder of the doctrine of internal secretions. In 1864 he described the syndrome following hemisection of the spinal cord which is known by his name.

I wish to read you abstracts from two of the cases which he quoted in studying this syndrome.

CASE 1—A drummer of the National Guard of Paris received a wound in the back of the neck. A sword thrown at him had penetrated the superior part of the right lateral half of the neck. An incomplete paralysis of movement took place in the right side of the body. In this case the surgeon had not examined the state of sensibility in the side where the patient had the power of movement, and, as the patient was not aware he had lost his sensibility, he had not spoken of it. Only the thirteenth day after he had been admitted in the hospital, having been pinched by a nurse who was playing with him, he found that he had lost his sensibility.

CASE 2—“Mrs W after a profuse haemorrhage became paralytic. Upon one side of the body there was a loss of sensibility, without, however, any corresponding diminution of power in the muscles of volition. The breast, too, upon that side partook of the insensibility, although the secretion of milk was as copious as the other. She could see the child sucking and swallowing, but she had no consciousness from feeling that the child was so occupied.

Upon the opposite side of the body there was defective power of motion, without however, any diminution of sensibility. The arm was incapable of supporting the child, the hand was powerless in its grasp. The leg was moved with difficulty and with the ordinary rotatory movement of a paralytic patient, but the power of sensation was so far

from being impaired that she constantly complained of an uncomfortable sense of heat, a painful tingling and more than the usual degree of uneasiness from pressure or other modes of slight mechanical violence”

Brown-Sequard summarized his findings in another case as follows “Three important facts, precisely like those I have discovered in animals after the transversal section of a lateral half of the spinal cord, existed in this case First, a morbid exaltation of sensibility in the side where movement was lost Second, a diminution of temperature in the side where the paralysis of sensibility existed Third, an increase in temperature in the side where the paralysis of movement existed”

He stated after a study of other cases, “To conclude I will say that any alteration of a lateral half of the cord, occupying its entire thickness, and able to produce paralysis, will cause First, a paralysis of movement in the same side and a paralysis of sensibility in the opposite side of the body, these two paralyses having the same extent Second, a paralysis of sensibility in the side of the body where the alteration exists and limited to the parts receiving their sensitive nerve fibers from the roots of the spinal nerves penetrating the cord in, or very little below, the altered portion

In the early days of clinical neurology when Brown-Sequard did his work, the findings in these cases of hemisection of the cord were of great importance They showed, for example, that the fibers in the dorsal columns do not cross in the cord The loss of vibration and sense of passive movement occurs on the side of the hemisection In a similar way the pyramidal fibers do not decussate in the cord, since the great majority have already crossed at the lower end of the medulla The pain temperature fibers cross in the first one or two segments above the point where they enter the spinal cord, and travel toward the brain in the ventral columns The loss of pain and temperature below the lesion is on the opposite side of the body Tactile sensibility is usually relatively well preserved since the fibers carrying this type of sensation run both in the ventrolateral and dorsal columns of the cord Some of these fibers cross in the cord whereas others run to the medulla in the dorsal column of the same side

Hassin, Kendrick and Connelly⁸ point out that the most common cause of the Brown-Sequard Syndrome in civil life is pressure on the

spinal cord by a tumor or syphilitic process while the rather uncommon cause is an inflammation of the spinal cord itself. Cases of syphilis which do not yield to energetic syphilitic treatment should be treated surgically. They are due not so much to direct injury of the spinal cord as to changes in the subarachnoid space. Adhesions here cause disturbances of the spinal circulation. Often after operation the function of the cord is improved.

Rand and Patterson¹⁸ state that stab wounds penetrating the spinal cord are not infrequently seen in large emergency hospitals. The initial symptoms are often those of a complete cord lesion. In the majority of cases, these symptoms change as time passes, usually becoming Brown-Sequard in type. The degree of recovery varies, depending largely upon the extent of the original cord injury.

Other cases are of course due to bullet wounds. Holmes⁹ in his lectures upon spinal injuries of warfare reported the study of forty-five cases of Brown-Sequard syndrome. He gave excellent typical examples. The interesting portion of the syndrome which is difficult to explain is the hyperesthesia which is often found upon the side of the body of the transected spinal cord. This is quite apparent in the history of the second case of Brown-Sequard's.

In one classical case described by Holmes with transection of the right side of the cord, the following changes were observed twenty-four hours after the wound. The patient complained of severe pain in the right leg, especially when it was touched or moved, and there was no local condition to account for it. Cotton wool appeared rough and tickled more on the right leg. Pin prick and all painful stimuli were "much sorer" than usual on the right side. Indeed hyperesthesia was marked.

Holmes stated that a homolateral hyperesthesia in Brown-Sequard cases is by no means constant, although he observed it occasionally. It extended over the whole half of the body almost to the segmental level of the injury. Here pin-prick, heavy pressure and especially scraping, or even rubbing hair clad parts with a wisp of cotton-wool, produced severe pain and much more reaction than these stimuli on normal parts. The application of cold, too, usually evolved pain, and heat of 45° C and upward caused a severe burning sensation. In one case pin-prick not only gave more discomfort than normal, but this

persisted abnormally long. This distant hyperesthesia always showed a tendency to diminish rapidly, and disappeared in some cases while the patients were under observation.

Holmes felt that, in many cases at least, the cause of the pain was to be found within the cord and that it was due to edema, circulatory disturbances, or slight diffuse lesions as Brown-Séquard originally postulated.

It has at times been suggested that fibers from the cerebral cortex have a controlling influence upon sensation not only at the level of thalamus but also in the cord. The hypothesis would suggest that these fibers are damaged, allowing overaction to sensory stimuli with the production of central pain. While this is a most attractive theory, it can be subjected to experimental proof only with difficulty.

In the case this morning the patient himself called our attention to an area of hyperesthesia over the right side of the back from the eighth to twelfth thoracic segments. He had noticed a spasm of the deep back muscles in this region. He also observed that heat and cold were unpleasant over this area, and that the muscles were sore to the touch. It can be demonstrated that heat, cold and pain are abnormally vivid over this area. Moreover the muscle spasm occurs on the side of the body where all the other muscles are hypotonic.

Since these symptoms have only been noticed for two years, it might be assumed that they represent an extension of the pathological process in the cord. There is one objection to this hypothesis. The area of hyperalgesia is not immediately adjacent to the area of loss of pain-temperature sensation, but is separated from it by several segments.

We have spoken about the hypotonia present on both sides of the body but more marked on the paralytic side. This fact may be emphasized, that the paralysis of the muscles on the side of the hemisection must always be flaccid even though it persists for years. The proprioceptive pathway in the posterior column is lost, and the long efferent pathways from the midbrain controlling postural tone have been injured as well as the corticospinal paths. The muscles are hypotonic, the reflexes not unusually active, and there is no clonus. The positive Babinski reflex gives conclusive evidence of injury to the corticospinal fibers.

CLINICAL DIAGNOSIS

There are few diseases to be considered in the differential diagnosis. Progressive muscular atrophy should come to mind. The atrophy and fibrillation more marked on the right side of the body, certainly indicate involvement of the anterior horn cells. Moreover, the corticospinal tracts are injured on both sides so that the condition might be considered combined upper and lower motor neurone disease or amyotrophic lateral sclerosis. In this disease any sensory changes are extremely uncommon. The marked sensory involvement shown in this patient would be unusual in the ordinary type of progressive muscular atrophy.

The question of an extra medullary tumor then arises. Certainly the tumor would have to spread over a large longitudinal area. In connection with this possibility it is important to state the facts that we have available concerning the progress of the pain-temperature loss. A careful neurological examination was done when the patient first visited this hospital in 1928. At that time the sensory changes on the right side of the body were similar to those found now. However on the left side there was at that time pain-temperature loss only over the skin area supplied by the sacral segments of the cord. In the intervening years the loss of pain-temperature sensation has spread upward on the left side to the fourth cervical segment.

This point is perhaps of some help in our diagnosis. When extra medullary tumors press upon the cord, the sensory changes are likely to appear first in the sacral region and spread up over the body. The anatomical explanation is simple. The sensory fibers from the lower portion of the body lie on the lateral edge of the cord. Those entering the cord at higher levels are placed progressively more mesially. Any pressure on the cord from without would injure first the more lateral fibers coming from the lower segments of the body.

Let us consider syringomyelia. We have shown that the right half of the lower cervical cord is practically functionless. There are also findings which indicate some involvement of the left half of the spinal cord. The picture is not unlike that found in syringomyelia but the progressive sensory loss from below upwards suggests some extra medullary process.

Could all the findings be dependent on syphilis of the spinal cord?

The blood Wassermann reaction is known to have been positive at the beginning of the illness, although it now has been negative for fifteen years. The spinal fluid Wassermann reaction was weakly positive when the patient was first seen here in 1928. Now it is negative. The patient has had rather active antisyphilitic treatment.

Perhaps it would be well at this point to hear the findings at operation. Will you please read the summary of these findings?

STUDENT The operation was performed under local anesthesia. The findings were described as follows:

"The laminae of the fourth, fifth and sixth cervical vertebrae were removed. The dura was very thick. On cutting through the dura a diffuse inflammatory process was encountered. This tissue was not cut because it might be attached to the cord. The field was enlarged from the third to the eighth cervical vertebrae. Above and below cerebrospinal fluid was encountered but the inflammatory membrane was present, although not as thick. The subarachnoid space was exposed.

"The cord presented a remarkable picture. There was a pocket on the right side of the cord in the region of the fourth and fifth cervical vertebrae and the cord was pushed to the left. Everywhere it was covered by a coat of inflammatory tissue and it looked as if it had been painted with a coat of white Duco. The inflammatory tissue was strong and tense and gave the appearance of a cyst. At the level of the lower part of the fifth cervical vertebra this cyst or rather the cerebrospinal fluid pocket disappeared and everywhere the cord was sealed. Proceedings from below upward an inflammatory membrane was cut about 2 mm thick. Coming upward to the region of the sixth vertebra the cerebrospinal fluid spaces were entirely sealed off again. The intervening band was dissected very carefully. On palpation of the cord there was a dense mass about 1 cm wide running transversely across the spinal cord very like an annular band. This mass was tightly drawn into the dorsal surface of the cord, and it was continuous above and below with the inflammatory mass which was dissected off from the underside of the dura. It dissected off fairly easily, although at times it was necessary to use a sharp dissection. The dura itself was probably three times its normal thickness. The annular band of fibrous tissue was split across the middle in the longitudinal plane of the cord. This incision passed through a small

corner of yellow tissue which looked like necrotic tissue and again it looked like an inclusion of a foreign body. The major reaction of the inflammatory tissue was around this central tiny mass which was probably 2 mm in diameter and roughly circular. This mass was then dissected from the dorsal surface of the cord, and it came off quite nicely from its entire dorsal aspect. There seemed to be nothing laterally, although the lateral cord was bound tightly to the dura just as it was above and below. There seemed no reason to dissect out the cord. It is surprising that there was no pain when the mass was dissected away, for usually the dorsal surface of the cord is very sensitive. The dura was left wide open to prevent a recurrence of the inflammatory mass over the cord."

What did the microscopic examination show?

There was not sufficient tissue to permit a diagnosis from study of the sections.

Although there was no satisfactory microscopic report, this picture is to me that of syphilitic meningomyelitis of the cervical portion of the spinal cord. This process most commonly occurs in the cervical region. You will note also that the inflammatory tissue was concentrated on the dorsal surface of the cord. This is typical of syphilitic meningomyelitis.

You are already aware that a syphilitic process of this kind may produce anatomical changes of great variability. Often there is sudden thrombosis of a large artery such as the anterior spinal artery. If this occurs in the upper cervical region, a sudden picture of complete flaccid paralysis appears (Ornsteen¹² and Margulis¹¹). The patients often improve slowly and may finally show a clinical picture of syringomyelia. When the cord is examined, a cavity is found in the central portion due to healing of the necrotic area (Tauber and Langworthy¹⁴). In the present case the onset of the disease does not suggest thrombosis of the anterior spinal artery.

If the thrombosis of the arteries occurs lower, in the thoracic portion of the spinal cord, both legs are suddenly paralyzed (Chung⁶ ⁷). Again this fairly common clinical picture does not fit our case.

Martin¹⁰ described the progressive muscular atrophy due to syphilis under the pathological title of amyotrophic meningomyelitis. He studied histological sections of the spinal cord. The cord was surrounded by a chronic meningitic process. There was thrombosis of

small vessels entering the cord which were involved in the meninges. The injury tended to work into the cord from the periphery, injuring the ventrolateral tracts and the anterior columns. This accounted for the involvement of the upper and lower motor neurones. In Martin's case there were few sensory changes.

We have little right to speculate concerning the pathological picture in the present instance. However there is certainly a chronic meningitis which probably caused thrombosis of some of the smaller arteries of the cord.

In connection with the suggestions for a clinical diagnosis which have been given, it is possible that all of them are to a certain extent correct, realizing always that the fundamental process is a syphilitic one. There is combined upper and lower neurone disease or amyotrophic lateral sclerosis dependent probably on changes in the cord similar to those described by Martin. There is also an extramedullary mass pressing on and constricting the cord as has been so clearly demonstrated at operation. We also know that the typical picture of syringomyelia may be produced by syphilis of the cord (Blumenthal, 1920). It is possible that a section of the spinal cord would show a large cavity. Finally the anatomical lesion presents the picture of a Brown-Sequard syndrome. The pathological diagnosis is syphilitic meningomyitis of the cervical portion of the spinal cord.

One wonders concerning the relation of the two injuries which the patient sustained to the localization of the syphilitic lesion. The first injury to the back occurred four years before the primary sore, and the second fifteen years after syphilis was contracted and five years before the onset of symptoms. It is known that in the experimental animal there is a tendency for syphilitic lesions to develop in a skin scar. The time of the injuries is not closely enough related to the syphilitic manifestations to be conclusive.

TREATMENT

Undoubtedly patients with similar complaints should receive intensive antisyphilitic treatment immediately after the diagnosis is made. If no improvement occurs, it is probably wise to operate and remove the thickened membrane in an effort to free the cord from constricting bands. In the present case the signs of cord injury were present for twelve years before the operation. During that time the

changes in the cord became so well established that no improvement could occur even when the pressure was removed. There has been little progress of symptoms in the eight years following the operation.

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Diseases of the Lungs

PULMONARY EMPHYSEMA¹

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THE structural changes that occur in the lungs in the development of pulmonary emphysema are well understood and this knowledge induces an attitude of futility in the treatment of this condition. If, however, we look upon pulmonary emphysema as an impairment of respiratory function we believe that much can be done for this large group of sufferers.

We have noted for many years that arrested cases of pulmonary tuberculosis return with symptoms suggesting a relapse. Physical examination tends to confirm the suspicions of the patient, but films of the chest reveal no change in the lesions, but do show evidences of emphysema. A few weeks of rest restores them to their previous normal, the physical signs are improved and repeated films show no change. Such patients have taxed their respiratory reserve to the breaking point.

Fluoroscopic and roentgenogram studies have added much in the recognition of pulmonary emphysema. Under the fluoroscope emphysematous lungs appear bright and the bases do not darken on complete expiration because the air cannot be expelled, the ribs tend to move up and down rather than to expand, the domes of the diaphragm are apt to be flattened and their excursion limited. In the lateral position the heart is separated from the sternum unless there are pericardial adhesions.

Stereoscopic films reveal additional stigmata of emphysema that

¹ From the Medical Department of the University of Cincinnati, Division of Tuberculosis. Drs James Christiansen, C W Hickam and J Schall of the Hamilton County Tuberculosis Sanatorium made the vital capacity measurements.

do not appear on fluoroscopic examination. The pulmonary arteries, as they pass through and emerge from the hilum shadows, are sharply outlined, the diaphragm domes are usually low and flattened, the ribs are widely separated. In the lung fields it is noted that the trunk markings are heavy and widely separated and may be distorted, particularly if there are present areas of fibrosis, emphysematous blebs may also be detected, especially in the bases. In the lateral view the anterior dark area is enlarged and separates the heart shadow from the sternum. The injection of iodized oil gives additional evidence of the presence of emphysema. The oil does not penetrate into the respiratory bronchus and alevoli and no stippling effect results. The oil is never found in the emphysematous blebs. The oil filled bronchi make their separation, distortion and dislocation much more obvious.

McCann¹ has found that when the residual air constituted more than 45 per cent of the total capacity a certain degree of anoxemia was almost invariably present. This is obviously sufficient to produce clinical symptoms, the exact level at which clinical symptoms may be produced is not known.

We felt that definite information regarding a patient's respiratory capacity would help to regulate his ability to work and in this way reduce the number of readmissions due to broken reserves rather than to an actual relapse of the tuberculosis.

The vital capacities of more than two hundred individuals has been measured and compared with their ability to work. The group included apparently healthy individuals in various age periods, uncomplicated cases of emphysema, pulmonary tuberculosis with and without emphysema and cases complicated by thoracoplasties, artificial pneumothoraces and phrenicotomies. Cases of known cardiac lesions were not included. While the number composing each group was not large the results showed such tremendous variations we were soon convinced that each case would have to be painstakingly worked out over a long period of time and that the measurement of one's vital capacity was not a short cut in anticipating one's ability to carry on sustained effort. Eight cases are here presented which show variations in vital capacities and ability to work.

CASE 1—Male, age thirty, had a complete paravertebral thoracoplasty on the right side with one third collapse of the left lung by artificial pneumothorax.

He worked in the laboratory eight hours daily without any apparent discomfort and without undue fatigue. He was never dyspneic and at no time was there evidence of cyanosis. Tidal air 427 cc, vital capacity 1305, complementary air 697 cc, supplemental air 180 cc.

CASE 2—Male, age fifty four, with less original involvement than the preceding case but with severe emphysema, was unable to do any work at all. Tidal air 675 cc, vital capacity 1170 cc, complementary air 405 cc, supplemental air 90 cc.

A comparison of these two cases clinically would suggest that the first was definitely more handicapped than the second, yet he was actually able to do far more work.

CASE 3—Male, age twenty eight, paravertebral thoracoplasty on the right side, was able to work for six hours on the wards mopping the floors. Tidal air 339 cc, vital capacity 1140 cc, complementary air 754 cc, supplemental air 247 cc.

CASE 4—Male, age fifty six, had severe emphysema, the tuberculous lesions had been arrested for many years, yet he was capable of only four hours of sustained effort. Tidal air 610 cc, vital capacity 2002 cc, complementary air 1294 cc, supplemental air 112 cc.

CASE 5—Male, age thirty four, had a good artificial pneumothorax on the left side with compensatory emphysema of the right lung. He worked six hours daily without undue fatigue. Tidal air 698 cc, vital capacity 3240 cc, complementary air 2430 cc, supplemental air 113 cc.

CASE 6—Male, age fifty six, had severe pulmonary emphysema without extensive tuberculous lesions, which were completely arrested. He was unable to carry on any ward work. Tidal air 652 cc, vital capacity 2835 cc, complementary air 2081 cc, supplemental air 101 cc.

A comparison of cases five and six, both of whom were in excellent physical condition, suggests there is a difference in the effects of compensatory and secondary emphysema.

CASE 7—Male, age forty seven, worked eight hours on the wards daily. Physical and roentgen ray examinations suggested that emphysema was far more serious than the tuberculous lesions which were well arrested. Tidal air 405 cc, vital capacity 1125 cc, complementary air 461 cc, supplemental air 259 cc.

CASE 8—Male, age fifty four, is the only case in this group that did not have pulmonary tuberculosis. Emphysema was marked, he became dyspneic after only a very short walk and there was slight cyanosis of the nail beds at times. He was totally disabled but insisted on using a typewriter for two hours daily, after which he was quite exhausted. Tidal air 281 cc, vital capacity 1012 cc, complementary air 562 cc, supplemental air 169 cc.

Cases 7 and 8 were quite comparable as to age and degree of emphysema, yet one was able to live and work comfortably while the other was almost totally disabled.

These cases are typical for the whole group. The evidence was convincing to us that we could not measure one's ability to work by studying respiratory function in this manner. That some individuals

are able to work two, four or eight hours before symptoms of fatigue appear suggests that time is important, and further suggests that the alveolar function of gas exchange represents the difference between two and eight hours' work when vital capacities are relatively the same

When emphysema is considered as diminished respiratory function, treatment of the condition has a definite objective. The patient understands that there is a respiratory handicap and that if he lives within that handicap life can be not only more comfortable but also definitely useful. The following case histories show the results of treatment over a period of years.

CASE 9.—Mrs M G, age fifty seven, examined first in May 1935, complained of fatigue and cough with expectoration of one ounce in twenty four hours of a mucopurulent sputum. The cough had been present for several years, worse in the winter and practically gone in the summer. Fatigue had been gradually getting worse until September 1935, when it was present on arising in the morning and became pronounced as the day advanced. She discovered that whiskey would revive her energy temporarily, finally she was dependent upon it to such an extent that she was under its influence almost constantly.

The positive physical findings were temperature 98, pulse 90, blood pressure 110 systolic, 84 diastolic, height 5'2", weight 100 lbs. The heart was not enlarged, the sounds apparently normal but there were frequent extra systoles. The percussion note was impaired over both apices anteriorly and posteriorly with hyperresonance over the bases, the rhomboid dullness was absent on both sides. The diaphragm dullness was low, the domes moved equally but only 3 cm on complete inspiration and expiration. Rales were heard in all lobes, more numerously over the bases and accompanied with asthmatic wheezes. Under the fluoroscope the lung fields were bright and clear, the midline structures normal, the domes were limited in motion and the bases failed to darken on expiration. The heart was separated slightly from the sternum in the lateral view. Stereoscopic films of the chest revealed minimal fibroid tuberculous lesions in both vertebral trunks, thickened pleural caps, heavy widely separated trunks in all lobes, prominent pulmonary arteries and low domes. The tuberculous lesions were arrested, the general picture was that of emphysema.

The Wassermann reaction was negative. Blood sedimentation index, 16 mm per first hour. Urinalysis was normal. The haemoglobin was 85 per cent with 5,680,000 red cells.

The patient was hospitalized and assured that whiskey would not be withdrawn. After the first week of complete rest she recognized that it was no longer essential and stopped its use. After four weeks the rales had disappeared and there was marked subjective improvement. Her liberties were gradually increased and during the course of a year it was found that she could do her usual duties for five hours without undue fatigue. Two or three hours of rest was followed by another five hour up period, after which she retired for the night.

It has been necessary to educate this patient that she has a functional

respiratory handicap and that if she lives within the limits of her strength living can be comfortable and she can live a useful life. The emphysema, of course, remains unchanged and she has been subject to some cough and expectoration in the winter as most of these patients are.

CASE 10.—Mrs. J. F., age forty-four, seen first in September 1932, complained of lack of endurance, frequent colds and a heaviness in the right chest when tired. An inactive tuberculous lesion involving the right upper lobe was discovered in 1926. In 1927 the appendix was removed and the uterus suspended. In 1931 her present complaints began to appear and because of the lesions in the right lung she thought she had relapsed but films of the chest were reported to her as remaining unchanged.

It was from her husband that the true picture was revealed. He stated that whereas formerly she was a devoted wife and mother, she was now constantly irritable with the children and things had reached such a state with him that he was seriously considering divorce.

The positive physical findings were temperature 98½, pulse 104, blood pressure 100 systolic, 70 diastolic, weight 98½ lbs. The heart was not enlarged, no murmurs were heard but there was an adventitious sound at the apex suggesting a pleuropericardial snap. The chest was not emphysematous in type. The percussion note was relatively normal, the domes moved equally with an excursion of 3 cm each. The breath sounds were rough over the right upper lobe posteriorly but no rales were heard at the bases. There was a harsh quality of the inspiratory phase, expiration was prolonged but inaudible over the bases. There was no evidence of cyanosis.

The Wassermann reaction was negative. The blood count and urinalysis were within the limits of normality.

Stereoscopic films of the chest showed low and flat diaphragm domes with tenting on the left side. The pulmonary arteries were prominent. Fibroid lesions containing calcification were seen in the vertebral, first and second interspace trunks of the upper right. The vertebral trunks of the upper left showed thickening. The trunks of both lungs were prominent and more widely separated than normal. A comparison of these films with those taken in 1926 and 1931 showed no extension of the tuberculous lesions but they did show further contraction of the scars. There was also noted an increasing flattening of the domes of the diaphragm and increased prominence of the pulmonary arteries and spreading of the trunks.

Under the fluoroscope the changes that we have noted in pulmonary emphysema were evident, namely, a limited diaphragmatic excursion, a failure of the lung bases to darken on expiration and separation of the heart from the sternum in the lateral view.

The first step in the management of this case was obtaining a sympathetic understanding on the husband's part that his wife's condition was due to fatigue and not due to any change in her affections for her family. After a month of absolute rest in bed the patient was permitted to be up for two hours at each meal time and was allowed to spend them doing what she wished to do. In the next six months it was found that she could carry on her normal duties for eight hours, when the heaviness in the right chest would become manifest. Two hours of rest then would restore her energy and the heaviness would disappear. Her chest distress warned her when she had passed her limit of endurance and served

as a constant reminder that she was definitely handicapped. No other treatment had been employed.

CASE 11—Mrs J N, age fifty eight, stated that she had been subject to attacks of asthma for twelve years. In the Spring and Fall months the longest attacks usually occurred but there was no season of the year when she would not have some wheezing. She was unable to associate the onset of the asthmatic attacks with anything except fatigue. Skin sensitization tests had always been reported to her as being negative. At the time of her first consultation she stated that she had not been entirely free from wheezing for two months and that adrenalin daily, and occasionally morphine had been necessary to bring relief.

The positive physical findings were temperature 98, pulse 110, blood pressure 120 systolic, 80 diastolic, weight 145 lbs, height 5'3". The heart was apparently normal. The chest suggested the emphysematous type. On palpation a definite lag was noted at the left base. Percussion revealed good resonance over the apices but the note was hyperresonant over both bases. The breath sounds were roughened over both apices and everywhere throughout the chest loud typical wheezes could be heard. Medium rales were heard just above the dome of the left diaphragm.

Urinalysis was within the limits of normal. The blood count showed 5,700,000 red cells per cmm. The Wassermann reaction was negative. Stereoscopic films of the chest suggested a thickened aorta, low flat diaphragm domes, heavy widely separated trunks, and prominent pulmonary arteries. Films of the nasal accessory sinuses suggested pathology in the ethmoid cells and both antra, which was confirmed by clinical examination. Fluoroscopic examination of the chest revealed limited diaphragmatic motion and fair darkening of the bases on complete expiration. Skin tests with the more common antigens were negative, but marked reactions were obtained from a hemolytic streptococcus, a non hemolytic staphylococcus and *Bacillus coli* obtained from sinus washings.

The treatment consisted of absolute bed rest for five weeks while the nasal sinuses were actively treated. In the next eight months the autogenous vaccine was given and extra hours of rest were employed. Occasional spells of wheezing occurred which were controlled by more rest. She then developed an attack which persisted for a month and which required several injections of adrenalin in each twenty four hour period.

Dr Meakins of Toronto had reported his observations on the use of abdominal belts in emphysema and it was decided to employ it in this instance. After fitting a tight belt the wheezing disappeared in twenty four hours and she remained entirely free from it for eleven months. After several days of wheezing a new belt was applied with complete disappearance of symptoms for ten months. The third new belt was as effective as the first two in controlling the symptoms. During this period of twenty one months the only treatment has been two hours of daily rest and the wearing of the belt except for occasional treatments of the nose.

The patient was so impressed with the results obtained from the belt that she wears it even in sleep. She states that she can breathe easier with the belt than without it.

Observations under the fluoroscope show that the diaphragm is slightly higher with the belt on and this no doubt accounts for her symptomatic relief.

Unfortunately the belt exerts its influence upon the pelvic floor as well as upon the diaphragm and there has recently developed a prolapse of the uterus

CASE 12—S V, age sixty three, was first examined in 1923. He was suffering at that time from hay fever (ragweed) and occasional attacks of asthma at night. During the course of examination an arrested, moderately advanced pulmonary tuberculosis was discovered, probably dating back to age nineteen when he had several pulmonary hemorrhages. He refused to believe that he has ever had tuberculosis, that it might be causing some disability because of the associated emphysema.

He was next seen in 1931. He had continued his regular work, but found it necessary to rest for long periods in several sanitariums. He had not been able to work for the preceding fifteen months. His complaints at that time were dyspnea on exertion, insomnia, fatigue, and inability to concentrate. The positive findings were temperature 98.6, pulse 82, blood pressure 160 systolic, 100 diastolic, weight 173 lbs, height 5'10". The chest was definitely of the emphysematous type, the movement of the ribs was limited and up and down rather than outward. Percussion revealed dullness over the upper left down to the fifth thoracic spine, and to the second thoracic spine on the right. The rhomboid dullness was absent on the left side. The right dome was higher than the left and fixed, the left dome moved only slightly on deep inspiration and complete expiration. Anteriorly the percussion note was impaired to the second rib on the left side. On auscultation the breath sounds were harsh with prolonged expiration over the upper left, where medium rales were heard on both inspiration and expiration. Over both bases expiration was long and almost inaudible but accompanied by wheezes at the left base. There were no rales or wheezes on the right side.

The heart sounds were essentially normal, occasional extra systoles were noted. The trachea deviated to the left.

The Wassermann reaction was negative. Urinalysis and the blood count were within normal limits. Stereoscopic films of the chest showed deviation of the trachea to the left, prominent pulmonary arteries and aorta, the heart was normal. The right diaphragm dome was flat and hitched to the lateral wall at the level of the eighth rib, the left diaphragm dome was flattened. The trunk markings were heavy and widely separated. Fibroid lesions were present in the vertebral, first and second interspace trunks of the left upper, and of the vertebral trunks of the right upper lobe. On fluoroscopic examination the lesions in the upper left were noted, the bases were bright and did not darken on complete expiration, the domes flattened on deep inspiration but actually moved very little. The heart was separated from the sternum on lateral exposure.

A comparison of the 1936 films with those taken in 1923 showed the tuberculous lesions more contracted but no more extensive. The trunks were more widely separated, the emphysema had progressed, especially on the left side where the tuberculous process had been more extensive.

The treatment consisted of rest and the application of an abdominal belt. The latter apparently improved the digestion but had little, if any, effect on the respiration. After two weeks of absolute bed rest he followed a schedule of four hours up, then two hours of rest, being up for a total of eleven or twelve hours daily. During this time up he occupies himself as he pleases and does as much work as he is able, but finds that he cannot endure any sustained effort.

Comparing the periods between 1923 and 1931 and from 1931 to the present time proves the effectiveness of his present routine. In the former period he would break down completely and spend months at a time in a sanitarium, while in the latter period he has felt relatively well and at no time has prolonged rest in bed been found necessary. The factors responsible for his emphysema will continue to operate, but we believe that its progression will be at a slower rate. If he continues to limit his activity in proportion to the decrease in his respiratory function life will be more comfortable.

COMMENT

When pulmonary emphysema develops in pace with the chronological age the principles of treatment suggested here evolve naturally. The aged deliberately slow up and do not unduly exert themselves. We must recognize more often than we do the fact that in younger individuals pulmonary emphysema represents prematurely old lungs and is accompanied by a variety of symptoms often simulating other conditions, particularly neurasthenia. They suffer from the "Tyranny of the Disease," that is, they are suspected of complaining to avoid work. These cases require careful and complete examination because emphysema is seldom found alone and uncomplicated.

CONCLUSIONS

Measurement of the vital capacity does not show the degree of disability resulting from pulmonary emphysema. Therefore each case must be studied individually and his ability to work determined by the method of trial and error.

REFERENCE

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ASPIRATION BRONCHOPNEUMONIA*

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THE consequences of inhaling various substances into the bronchi and lungs provide a subject for interesting study and of vital importance for many patients. Bronchopneumonia is one of these consequences, and the discussion is centered about it. The cases which I am presenting illustrate certain circumstances under which this may occur, the management of the case after it does occur, and, especially, the possibilities and means of prevention. The matter is of significance in most branches of medical practice since aspiration bronchopneumonia sometimes is the termination of various illnesses and sometimes may intervene to turn the tide unfavorably, when otherwise recovery would be expected.

Primarily it is necessary to have an understanding of the mechanisms which enter into the pathogenesis of aspiration bronchopneumonia. The process is initiated by the inhalation and retention of substances foreign to the lower respiratory tract. In health this is prevented by the screening and straining effect of the nasal passages, by the flow of mucus here and through the channels of the throat, trachea, and bronchi, by the operation of reflexes in the pharynx and larynx to divert substances into the esophagus, by the action of reflexes to initiate expulsive coughing, and by other mechanisms of ciliary action and phagocytosis. These protections are so efficient that gross material is seldom inhaled and, if inhaled, is promptly and effectively expelled or disposed of so that no harm results. Circumstances which explain the occasional failure of the normally ample protections and the results of that failure may logically be discussed under the following divisions —

1 Conditions favoring inhalation or aspiration of substances foreign to the lower respiratory tract

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- 2 Conditions favoring lodgment or retention of such substances
- 3 Types of inflammation which result and factors which influence these

CONDITIONS FAVORING ASPIRATION

The conditions which favor the inhalation of foreign material have to do mainly with the impairment of the protective reflexes of the pharynx, larynx, trachea and bronchi. Probably the most common circumstance under which this occurs is unconsciousness. During deep sleep, particularly under the influence of hypnotic drugs, the reflexes may be dulled. We have introduced iodized oil into the mouths or nasopharynges of sleeping patients and, by roentgenography, found gross traces of it in the bronchi and pulmonary alveoli the next morning. Saliva or other liquid in the mouth or pharynx would behave similarly. The same experiment has yielded similar results in patients in alcoholic stupor, a condition in which the protective barriers are profoundly disabled. Likewise, the unconscious states of epilepsy, apoplexy, or asphyxia, may lead to aspiration of material from the pharynx. The same may be said of deep anesthesia, particularly when it is induced by anesthetics such as ether which produce much salivation and bronchorrhea. Generally speaking, the reflexes are much more lively in healthy children, which helps to account for the infrequency of aspiration bronchopneumonia in this age group.

Various other factors may in time result in a dulling of the protective reflexes. As suggested above, increasing age may be responsible, and this is especially true in the enfeebled states of senility. It seems possible that chronic infection of the paranasal sinuses with prolonged drainage of discharge into the nasopharynx may lead to a dulling of the reflexes or at least to a conditioning of these so that they do not respond very actively and thus permit the aspiration of material below the larynx. In unusual cases of chronic cardiospasm with dilatation and inflammation of the esophagus, dulling of the reflexes results and some of these patients habitually regurgitate and inhale esophageal contents and eventually develop chronic or subacute bronchopneumonia.

The topical application of local anesthetics in the nasopharynx and larynx likewise may temporarily nullify the reflex mechanism.

and permit aspiration of material into the lower passages. This seems particularly true if the faucial pillars are anesthetized. Radiopaque fluids, such as iodized oil, may be dropped on the back of the tongue after such anesthetization, and then, when the patient swallows, some of it may be seen fluoroscopically entering the trachea and bronchia. I have seen a case of fatal aspiration pneumonia which resulted, after an operation on the larynx, from the drinking of a cup of coffee while the pharynx and larynx were still thoroughly insensitive from the local anesthetic.

Other familiar mechanisms are choking during eating, aspiration during submersion, any sudden gush of fluid into the pharynx, (very well illustrated in one of the cases I am presenting), and trauma leading to damage of the normal neuromuscular mechanisms. Impairment of these mechanisms may be seen in rare situations such as diphtheritic neuritis and injury to the ninth, tenth, and eleventh cranial nerves at their point of emergence. Pulmonary complications under the latter circumstance were observed after gunshot wounds during the World War.

Other unusual conditions, such as a carcinomatous fistula between the esophagus and trachea or bronchus, may lead to aspiration bronchopneumonia. The foreign substance is esophageal contents which leaks through the fistula and is inhaled or gravitates into the bronchi and lungs.

CONDITIONS FAVORING RETENTION

The second line of defense, if the other safeguards have failed to prevent the aspiration of foreign material into the lower respiratory tract, consists of the mechanisms of coughing, bronchorrhea, ciliary action and phagocytosis which, when effective, act to expel or dispose of the material. Dust, bacteria and other impalpable particles are more or less constantly inhaled, and, were it not for the high efficiency of these mechanisms, few people could long survive the resulting damage to the lungs. Operating mostly on the autonomic level, the physiologic protection is usually effective in the sleeping and waking states. Occasionally, however, conditions intervene more or less to disable or paralyze even this line of defense.

In states of profound and lasting unconsciousness, such as those due to general anesthesia, alcoholic intoxication, trauma of the skull,

FIG. 1



September 29, 1936 (two weeks after onset) Bronchiopneumonia represented by faint mottling in the right lung, field especially in the first interspace, bronchiopneumonia in the left lung becoming confluent in the middle third where the small ruractions indicate beginning multiple abscess formation

FIG. 2



October 5, 1936 Bronchiopneumonia slightly more intense in the right lung. In the left lung, in addition to the bronchiopneumonia at the beginning, formation of a large abscess is indicated by the round density in the middle third with the ruraction and fluid level

Fig 3



Fig 4



October 14 1936 Almost complete resolution of the bronchopneumonia has occurred on the right and in the upper lobe. The abscesses with its fluid level and surrounding suppulsive pneumonia is clearly indicated in the middle of the left lung field.

Lateral roentgenogram October 14 1936 indicates the position of the abscesses in the upper lobe

asphyxia and apoplexy, aspirated material may be retained in the bronchi or air vesicles. The expulsive mechanism may likewise be impaired on account of weakness during debilitating illness.

Preexisting damage of the lung attributable to previous inflammations, inhalation of silica dust and the like, often favors the retention of foreign material and consequently the development of new inflammation. The old damage is manifested principally by fibrosis and emphysema of the lung which is now inefficient not only for respiration but also for the disposal of foreign material which may enter it.

Impairment of the integrity or function of the diaphragm or chest wall sometimes permits lodgment of foreign materials. If the diaphragm has been immobilized by pleuritic adhesions or paralyzed as a result of diphtheritic neuritis or the destructive action of a tumor along the course of the phrenic nerve, the important piston effect of this muscle is lost, the effectiveness of coughing is weakened, and the expulsion of material from the bronchi is impeded. The temporary splinting of the diaphragm after operations on the upper abdomen or after trauma of the thoracic wall is recognized as a somewhat similar factor in the development of postoperative pneumonia and pulmonary atelectasis.

Abnormal conditions causing stenosis or stricture of the lower respiratory passages, if they persist, inevitably lead to impairment of the mechanisms which usually dispose of infectious and foreign material from the lung and consequently to inflammation. I have observed chronic organizing pneumonia in a woman with stenosis and malacia of the trachea caused by the prolonged pressure of a retrosternal thyroid tumor. The development of subacute and chronic organizing pneumonia secondary to stenosis of the left bronchus from the pressure of an aortic aneurysm is a familiar picture.

The use of topical anesthetics in the trachea and large bronchi may temporarily nullify the coughing reflex and one may conceive of many other mechanisms which may permit the lodgment of foreign material in the lower respiratory tract.

The inflammation resulting from the retention of aspirated material may be due at first to the irritating properties of the material itself. However, in time, infection is inevitably associated with the process. Some of the organisms almost continually inhaled with

the inspired air, ordinarily harmless and easily disposed of, may now become definitely noxious. Other sources of infection are principally in the mouth and nasopharynx. The crypts of the tonsils and other adenoid tissue of the nasopharynx may harbor myriads of organisms, the same is sometimes true of chronically or acutely infected paranasal sinuses. Likewise, more or less extensive collections of organisms are present about the gums and teeth.

TYPES OF INFLAMMATION RESULTING FROM ASPIRATION

Inflammation caused by the aspiration and retention of extraneous matter varies from a simple exudate to gangrene. Ordinarily the first reaction of the bronchial mucous membrane is the pouring out of mucus which may be sufficient to sweep away the foreign material. If not, swelling and reddening of the mucosa at the site of lodgment develop, rapidly subsiding if the offending cause is promptly removed. If the foreign material is of such consistency as to permit its entrance into and lodgment in the alveoli, inflammation may also appear early as an exudative lobular pneumonia. This may be mild and associated only with bacteria of low pathogenicity such as pneumococci, micrococci catarrhalis, and other organisms harbored in the respiratory tracts of most healthy people. Such simple bronchopneumonia or lobular pneumonia, if limited, may resolve quickly, causing little disability. Foreign material of more irritating properties, such as gastric juice, leads to more intense bronchopulmonary inflammation, and, from the start or later, this may be associated with the invasion of more virulent organisms such as streptococci or anaerobic bacteria from the mouth or nasopharynx. In this event the bronchopneumonia is likely to become suppurative with actual destruction of small or large sections of the bronchial and parenchymal structure. Such a process may be arrested at any time in its course, but often goes on to abscess formation, as illustrated in one of our cases. Gangrene of the lung, which in this service is identified as death of pulmonary tissue *en masse* without the formation of an abscess membrane at the periphery of the process is not a common occurrence but a very fatal one. In our experience it has been observed most often in patients who, during a drunken stupor, aspirated vomitus into the lung and retained it there during a considerable period of unconsciousness. These subjects have ex-

FIG. 5

531R



FIG. 6

3059, 432R



October 29 1936 Resolution of the purulent pneumonia and shrinkage of the abscess cavity which is still indicated however by the central indentation

December 18 1936 Complete disappearance of the abscess & the residual strand like organized fibrous tissue extends from the hilum at the site of the abscess



tensive infection of the mouth and nasopharynx with anaerobic organisms. With the usual exception of gangrene, any of these processes may become arrested at any phase of their development. Resolution of inflammation may be complete. Protracted or suppurative inflammations almost always leave some damage such as chronic organizing pneumonia, pulmonary and pleural fibrosis, and sometimes bronchiectasis. In such residual lesions, invading organisms may be harbored indefinitely and give rise to a renewal of inflammation, especially after subsequent acute respiratory infections.

The extent and intensity of the inflammation depend on a combination of factors. The aspiration of clean water during swimming or swallowing seldom is harmful and at worst it is not likely to cause more than a slight passing inflammation, but if the water is contaminated the results may be serious. I have seen patients suffer from lung abscess because necrotic material from around the teeth was aspirated with the water, and similar occurrences in men who swam in water heavily polluted with sewage. It is obvious, therefore, that the irritating quality of the aspirated material and the concentration and character of the bacteria have an important bearing on the process. Likewise, the physical form of the aspirated material is important. The aspiration of a coherent mass of necrotic matter, heavily laden with anaerobic bacteria, from a tonsillar crypt or a peridental abscess is likely to lead rapidly to acute suppurative pneumonia about the point of retention, and this in a few days will be manifested as an acute lung abscess. On the contrary, the aspiration of considerable amounts of blood from the mouth or throat is more likely to produce diffuse bilateral lobular pneumonia because the fluidity of the material permits it to filter, far and wide, into the alveoli, and the transported organisms are suspended in weaker dilution. The bulk of the aspirated mass in relation to the calibre of the bronchi also has an important bearing. A small mass of necrotic material usually lodges in a small bronchus and the resulting initial inflammation is likely to be limited. A larger mass cannot be aspirated so deeply, and if it lodges in and obstructs a large bronchus, a whole lobe or even a whole lung may become involved with suppurative pneumonia. This is observed more frequently following the aspiration of gross material such as an extracted tooth or a foreign body from outside. The effects of aspiration sometimes

may be minimized if drainage from the inflammatory process is adequate and free through the bronchi. If the aspirated material is expelled before the inflammation is too advanced, the channel of drainage may be cleared sufficiently to permit resolution and healing. Continued obstruction, however, almost assures that the process will go on to suppuration.

RECOGNITION OF ASPIRATION BRONCHOPNEUMONIA

The diagnosis of this condition, once established, depends on familiar methods of observation. Recognition of the occurrence at its very start, however, may accomplish a great deal in preventing serious consequences. In the first place, the fundamental conceptions described above permit the recognition of conditions which may favor or allow the aspiration of foreign material, and on these grounds it may be suspected early if the patient has any unusual symptoms such as cough, dyspnea and wheezing. Unexplained wheezing in an acute illness with other symptoms pointing to the lower respiratory tract always raises the question whether the bronchial passages are obstructed. Examination may reveal widespread rhonchi and wheezing rales due to diffuse inflammation and swelling of the bronchial mucosa, but in other cases these sounds will be heard only over a section of one lung when the possibility of blockage of the bronchi on that side may be even more strongly suggested. With unilateral obstruction the sounds usually are detected most prominently in the middle of the interscapular region on that side. In such cases the wheezing may be referable to an accumulation of sticky mucus at or around the point of obstruction or swelling in the bronchial mucosa. Occasionally bronchoscopy is warranted and may result in the finding of the aspirated substance and its removal. The diagnosis of the subsequent developments depends on the nature, rate and intensity of the inflammatory changes, and is not discussed here.

THE AVOIDANCE AND TREATMENT OF ASPIRATION BRONCHOPNEUMONIA

The means of avoiding or preventing this condition are obvious if one understands the pathogenesis. The most practical action is to eliminate extensive foci of infection in the mouth and nasopharynx. Dental hygiene with regular brushing of the teeth is sufficient to

cleanse away gross collections of necrotic material, but in some cases, additional measures for prophylaxis and treatment are necessary. If the tonsils are extensively diseased their removal as a safeguard is occasionally indicated, and active treatment of infectious foci in the nose and paranasal sinuses likewise may be required. In a number of large surgical clinics strict preoperative attention to the condition of the mouth and nasopharynx and suitable prophylactic treatment has reduced greatly the incidence of postoperative pulmonary complications. The same precautions are clearly indicated as a matter of routine personal hygiene, but particularly when the general health is impaired and the action of the protective mechanisms of the respiratory tract are likely to be disabled or interfered with. The treatment of bronchopneumonia is well known. In some cases, therapy may be directed against a specific invading organism, but as a rule a number are present. As mentioned, bronchoscopy for the removal of retained material may be indicated in the early stages in a few cases. If the process goes on to suppuration then the importance of postural drainage for the elimination of purulent discharges through the bronchi should be recognized. The principles of treatment are those applying to the general class of suppurative pneumonia and lung abscess. If postural drainage does not induce sufficient flow of discharges it may be necessary to remove them by bronchoscopy and suction. Localization of the process and the formation of pulmonary abscess may require thoracotomy and surgical drainage. Recovery should be followed by a long period (three to six months) of convalescent treatment in order to avoid chronic inflammation or to prevent wide destructive effects and recurrence if the inflammation has already become chronic.

SUMMARY

Because of the efficiency of the physiologic safeguards, noxious foreign substance usually does not lodge and cause harm in the bronchi and lungs. Otherwise, the secretions from the mouth and nasopharynx, laden with bacteria, would be a constant menace.

Conditions which lead to failure of these safeguards are described.

The pathogenesis and development of the various grades of bron-

chopulmonary inflammation resulting from such failure are described and illustrated by case histories

Suggestions are offered for the early recognition and treatment of aspiration bronchopneumonia

The advantage of recognizing the conditions in which aspiration may occur, of anticipating the possibility, and of using measures to prevent it or its serious consequences, are especially emphasized

CASES

J J, a male, American Indian, aged forty two, developed a sore throat about November 22, 1936. He visited a clinic and was given a solution for gargling, but the soreness increased rapidly until he was unable to swallow without great pain. He entered Bellevue Hospital, November 26, where he was found to have a left peritonsillar abscess. Without the use of anesthesia, the abscess was incised, resulting in a gush of yellow, non odorous pus. At the same time, the patient coughed and had a strangling sensation in the throat, but these symptoms promptly subsided. In the next twenty four to forty eight hours he developed a cough which was productive of a small amount of mucopurulent sputum, and three days after the operation he complained of a sharp pain in the left chest, and a day later, less severe pain in the lower part of the right chest. The pain did not continue and the patient left the hospital, December 1. Cough and expectoration increased rapidly, he felt generally unwell and returned to the hospital the next day. He was expectorating six ounces of non odorous purulent or mucopurulent sputum a day. He complained of slight substernal pain on coughing, did not feel chilly, but stated he had hot spells and occasionally sweated profusely. Physical examination at this time showed a very well developed, muscular man of stocky build, who was coughing and expectorating frequently. Except for the following findings, no abnormalities were recorded. Many teeth were missing and a number of stumps of carious teeth were surrounded by a severe inflammatory swelling of the gums, pus could be expressed on pressure at these points. The swelling in the tonsillar region had entirely subsided and there was only moderate hypertrophy and a deeply cryptic appearance of the tonsils. The pharynx was congested. The submaxillary and cervical lymph nodes (anterior and posterior) were moderately enlarged, especially on the left. There were several small scars from old lacerations of the face and arms. Auscultation revealed showers of small moist rales below the third interspace on the left extending to the base anteriorly and to the midaxillary line laterally. The temperature was 102.2°, pulse rate 90 per minute, respiratory rate 20 per minute, blood pressure, 126 mm mercury systolic, 80 diastolic. A roentgenogram taken two days later showed patchy mottling with a few moth-eaten rarefactions in the lower half of the left lung field and a light irregular mottling extending outward from the level of the hilum on the right. The blood count showed 10,700 leukocytes, 45 per cent polymorpho nuclear neutrophiles, 20 per cent lymphocytes, 19 per cent transitionals, 5 per cent mononuclears, 1 per cent eosinophiles, 2 per cent basophiles, 4,700,000 red blood cells. The urine showed a trace of albumin, the blood Wassermann test was negative. During his stay in the hospital the patient has never appeared acutely ill. The temperature ranged from 100.4° to 103° during the first week, gradually

subsided during the next three weeks, and since then has not been above normal. The pulse rate at first ranged from 100 to 110 per minute, later from 72 to 90. Respirations ranged from 18 to 22 per minute. The sputum varied from one to six ounces daily, much of this being expectorated during postural drainage which was carried out from fifteen to twenty minutes three times daily. The mucopurulent character gradually became less prominent, and on February 1, 1937, the patient was raising less than half an ounce of foamy mucoid sputum. Three cultures of the sputum showed a mixture of *streptococcus viridans*, *streptococcus hemolyticus*, *micrococcus catarrhalis* and a gram negative bacillus. No fusiform or spirochaetal organisms or acid fast bacilli were ever demonstrated. Various polymorphonuclear and mononuclear cells were seen microscopically in the stained smear. In spite of the symptomatic improvement, examination shows at the present time (February 1, 1937), numerous crepitant rales on deep inspiration, slightly increased by coughing, below the fourth rib and the angle of the scapula on the left, mostly anteriorly. A few crepitant rales are heard also at the base of the right lung posteriorly. Roentgenograms taken at intervals of about two weeks demonstrate slight diminution in the patchy mottling of the lungs but there is still considerable residue.

Comment—This is considered to be a case of aspiration suppurative bronchopneumonia due to the inhalation of pus into both lungs, especially the left, when a peritonsillar abscess was incised. Pulmonary inflammation has been present for nine weeks and from the character of the sputum and the roentgen ray appearance seems to be associated with small areas of necrosis and abscess formation. The streptococcus is a fairly common cause of such a process, and seems to be the chief offender here. It is anticipated that gradual resolution will occur but also that fibrous organization will take place and that the patient should have at least six months of convalescence to promote reasonably dependable healing. It is also anticipated that a certain amount of permanent damage will result and that this later will manifest itself as a localized pulmonary fibrosis with or without bronchiectasis. Aspiration could have been avoided had the patient been placed in position so that, when the abscess was opened, the discharged pus would have drained away completely through the mouth.

A B, a white woman, aged thirty, being in labor, was admitted to the Obstetrical Service of Bellevue Hospital, September 14, 1936, the duration of gestation having been estimated to be thirty eight weeks. She had visited the Out patient Clinic, June 22, 1936, and was then found to be in good health except for a history of hay fever for the previous fifteen years, her teeth were reported to be in very poor condition. The patient had had one previous normal pregnancy and another child, stillborn seventeen months before. The blood Wassermann test was negative. Labor started at 6 p.m., September 14, and the second stage was pro-

longed due to failure of advancement of the fetus. Delivery of an eight pound, thirteen ounce baby was finally accomplished at 3:14 a.m., September 15, by resort to episiotomy and the use of high forceps for rotation and extraction. Previous to this, rectal analgesia was administered, and during the operation, ether anesthesia. The patient vomited several times during the anesthesia and immediately afterwards. The placenta was delivered at 3:18 a.m., the loss of blood being estimated at 800 cc. One hour later, Magendie solution, m/v, was given hypodermatically, at this time the temperature was 90.8°, pulse rate 120 per minute, respiration 24 per minute. She was returned to the ward at 6:45 a.m., when the pulse was 120 per minute and weak. The patient was sweating and somewhat cyanotic, and the breathing was noisy and rapid. She was given a hypodermic clysis and an infusion of glucose solution. Later in the day she complained of tightness in the chest and throat, hoarseness, and soreness on swallowing. There was a frequent dry cough during the next thirty-six hours. Examination during the first two days revealed severe gingivitis and pyorrhea. The patient was quite dyspneic and wheezing, and the respiratory rate was as high as 35 per minute. She used the accessory muscles of respiration, and the alae nasi dilated during inspiration. The breath had a foul odor. Breath sounds were diminished on the right and numerous moist, sonorous and sibilant rales were heard throughout both lungs during inspiration and expiration. There was no dullness. The temperature rapidly rose to 102.4°, and the pulse rate varied from 96 to 150 per minute. The white blood count, September 16, was 17,050. Treatment consisted of the use of the eroup tent and the administration of ephedrin, codeine, aspirin and ergot. For the next five weeks the patient was very ill. During the first week, hoarseness and soreness in the throat and chest gradually subsided and the wheezing became less pronounced. The patient began to expectorate green sputum September 18, four days later, the color changed from green to yellow, and the quantity increased to four or five ounces a day. Three weeks after the onset, the sputum had a definitely foul odor, was greenish brown in color and amounted to six or eight ounces in twenty-four hours. During the first week there was considerable abdominal distension. The temperature ranged intermittently from 98.4° to 103°, but usually the daily rise was not above 101.5°. The respiratory rate varied from 20 to 24, and the pulse from 90 to 120 per minute. The white blood counts and the polymorphonuclear neutrophile ratios during the acute phase were as follows: September 20, 12,600, 75 per cent; September 22, 20,750, 77 per cent; September 30, 22,150, 80 per cent. The red blood count which was 4,550,000, with 75 per cent hemoglobin on admission, dropped rapidly until by September 20, it was 2,100,000 with 65 per cent hemoglobin. Physical examination from time to time revealed a gradual diminution of the wheezing rhonchi during the first week, and, after this, harsh breath sounds, small and medium moist rales, usually in the lower two thirds of both lungs. Slight dullness was elicited in the lower half of the left anteriorly and posteriorly. The patient received a transfusion of 500 cc. blood September 17, and a 5 per cent glucose infusion (1000 cc.) September 22. She was transferred to the Chest Service on October 6. The observations recorded above and the roentgenograms of the chest (figs 1 and 2) taken September 29 and October 5, lead to the diagnosis of bronchopneumonia due to aspiration of vomitus and infectious material from the mouth during anesthesia. Both lungs were involved, particularly the left where, in the lower half, the beginning of abscess formation is demonstrated clearly on the roentgenograms. Further elimi-

cal and roentgenographic observation demonstrated a gradual resolution of the bronchopneumonia in the right lung and partial resolution on the left, but a definite abscess formation in the middle of the left upper lobe (figs 3 and 4). The patient continued to have copious foul sputum which, on aerobic culture, showed the presence of *streptococcus viridans* and a hemolytic *staphylococcus*. Anaerobic culture was not made but anaerobic organisms were assumed to be present also. Bronchoscopy, performed October 14, showed reddening and thickening of the walls of the bronchi on the left and of the right middle lobe bronchus. Further study of the teeth and gums showed a subacute Vincent's infection. It was anticipated that surgical drainage of the pulmonary abscess by thoracotomy would be necessary, but the patient took a turn for the better on October 21, and improvement continued afterwards. The sputum rapidly diminished and lost its foul odor, changing in character from mucopurulent to mucoid by December 21, when the amount was only one ounce a day. Streaks of blood appeared in the sputum only on one occasion (October 16). The temperature dropped slowly and did not rise above normal after the tenth week. The white blood count was 16,150, with 78 per cent polymorphonuclear neutrophiles, October 10, and 12,700, with 80 per cent, on October 21. The urine showed a trace of albumin, October 7. The red blood count September 22, was 3,970,000, hemoglobin 60 per cent. The patient's general condition improved strikingly. From October 26 onward, the only signs elicited in the chest were harsh breath sounds and occasionally a few rales in the left upper lobe. From the first part of October onward, the patient assumed an inverted posture for natural drainage of the contents of the abscess for fifteen to twenty minutes three times daily. There was no medication except an occasional dose of codeine for the cough. As shown in the roentgenograms (figs 5 and 6) resolution of the pulmonary inflammation and contraction of the abscess cavity was well under way by October 29. By December 18, the abscess cavity was completely obliterated, and only heavy strands of fibrosis remained to mark the site of the lesion. These were present also at the time of the patient's discharge from the hospital, January 15, 1937. She left to go to the country, having been advised to take another two to three months for convalescence. This was urged because of the knowledge that, in such cases, infection remains latent in the lung indefinitely and ample time must be given to insure permanent healing.

Comment—In this case intense acute inflammation was set up in the bronchi and lungs by the aspiration of irritating gastric contents. Infection promptly supervened, at first presumably with the common aerobic organisms present in the nose, throat and respiratory tree, but later with anaerobic organisms also, which usually account for the foul sputum. Subsequent developments illustrate strikingly the various grades of aspiration bronchopneumonia. Presumably the quantity of irritating substance inhaled into the bronchi and alveoli of the right lung was small, consequently there was only a scattered patchy bronchopneumonia which resolved rapidly and completely. On the left the concentration of the irritating foreign material was greater, and the inflammation proportionately severe.

Instead of resolving, the process went on to suppuration, at first with the formation of small multiple abscesses which later coalesced into a large one. The natural healing by resolution progressed rapidly, once started, but there was also organization which left a presumably permanent fibrosis. There may be some associated bronchiectasis, and it is to be expected in such a case that acute respiratory infections may lead readily to bronchitis in this region, which may be more severe and more protracted than it would be in the healthy lung. The means of prevention of such a serious complication are obvious. Infectious foci in the mouth and upper respiratory tract should always be cleansed or removed in cases where unconsciousness from any cause, such as anesthesia, is to be anticipated. Also, during the unconscious state precautions should be taken to avoid the aspiration of vomitus or other material accumulating in the mouth or throat.

Diseases of Heart and Circulation

CORONARY THROMBOSIS AND CARDIAC INFARCTION

A Clinical Presentation, with Some Remarks upon Etiological Factors Diagnostic Criteria, Prognostic Data and Therapeutic Methods

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I HAVE the temerity to discuss the subject of coronary thrombosis and cardiac infarction even though it has been dwelt upon so often that to some it may seem thread-bare. There may be a few unfortunate physicians and some blasé students who feel that so much has already been said on the subject, and so well said, that little remains of value to be said. To them any further remarks may be boresome. For such spiritually dissipated individuals, no subject long holds the full life sustaining thrill. It is true perhaps that the typical dramatic clinical picture of coronary thrombosis is now so generally well known that laymen make the diagnosis often quite correctly and some pharmacists may prescribe aminophyllin. Nevertheless, conscientious physicians and thorough students realize that there is still much to be learned concerning many phases of coronary thrombosis and cardiac infarction.

It is widely recognized that the clinical picture, though generally clear cut, may be simulated by other conditions and when atypical may be missed or overlooked. Most often the diagnostic errors of commission barely balance the errors of omission. There is furthermore no universally applicable always successful therapeutic regime.

Most internists have clinical impressions which are usually supported by observations on a few carefully studied cases and these notions even though unproven may be worth setting forth from time to time. The hope is that others will make similar studies on their

patients and add supportive evidence or proof for or against the validity of the opinion

The *etiology*, the predisposing and the precipitating factors, the prognostic criteria and the therapeutic indications should all be commented upon. As primary *etiological factor* coronary arteriosclerosis apparently provides the background for thrombosis in the majority of cases but a coronary arteritis is being recognized more frequently as a basis for thrombosis in younger individuals. The *precipitating factors*, however, are often obscure. Occasionally there seems to be definite relationship to an acute general infection such as influenza and perhaps also the one-time popular newspaper designation of death from acute indigestion has incriminated overeating. On this basis and others, Werley has concluded that food allergy is a factor. Trauma has not been accorded due emphasis as a precipitating factor and I believe that stress or strain must be included among the immediate causes of the thrombotic states in the coronary arteries.

The matter of *prognosis* in the patient with coronary thrombosis depends of course upon the extent of the myocardial infarction. The ways and means of judging this quantitatively are still rather crude and contributions to our knowledge in this direction are desirable. Massive cardiac infarction and consequently a grave prognosis are considered to be indicated by (1) The persistence of substernal pain for more than two hours, (2) a conspicuous drop in the systolic blood pressure, extreme hypodynamic heart failure, cardiac dilatation, shock, collapse, (3) considerable febrile reaction over 101° of fever persisting for more than four days, (5) a high leukocytosis of 20,000 or more for four days or more, (6) more than 30 per cent non-filamented forms, (7) less than 1 per cent of eosinophiles, (8) the appearance of mechanism disorders as alternation or gallop rhythm, paroxysmal ventricular tachycardia, heart block of auriculoventricular or intraventricular localization, (9) the prompt development of loud murmurs or friction rubs, (10) the occurrence of cardiac asthma or congestive failure or of embolism.

A leukocytosis of 20,000 or more, particularly if the percentage of non-filamented forms remains above 30 per cent after the fourth day and if the eosinophiles are absent or do not rise above 15 per cent, has been suggested by Goodrich and Smith¹ to forebode a fatal issue. Likewise, the sharply rising erythrocyte sedimentation rates

that continue to increase to high levels before the fourth day have been considered evidences of most hopeless outlook while a slow rise and a gradual decline in the erythrocyte sedimentation rate are favorable, according to Shookhoff, Douglas and Rabinowitz² Steinberg³ found a rising and persistently high blood nonprotein nitrogen to be of grave prognostic significance

Some observations with respect to these laboratory findings as well as some newer evidence of the creatine content of the blood and of the urine will be presented in the discussion of the clinical case record of a patient who survived what was apparently a massive cardiac infarction. The importance of electrocardiographic changes will be briefly commented upon.

Treatment perhaps needs little discussion for it is almost universally recognized that a half grain dose of morphine is usually necessary and adequate to relieve completely the pain. Still there are some who persist in giving small doses of milder narcotic or even trying non-narcotic analgesics. However, the therapeutic efforts necessary for the control of complicating pulmonary edema and for the relief of a stubborn abdominal distention may well be touched upon again. A favorable outcome in a case may be dependent upon careful attention to every detail of the patient's condition.

In order to present some experiences, observations and data upon these questions, I will take as a text a clinical case that I have recently studied in some detail. One case history only will be presented in detail.

CASE HISTORY

F. A. B., aged forty two, a young buyer for a wholesale grocery company, came under observation as an emergency case on August 8, 1936, at about 7:30 p.m. When first seen he was prostrated and complaining of severe gripping pain under the midsternum, a choking sensation and an inability to get enough fresh air. He considered his trouble to be acute indigestion although he had not eaten for some six or seven hours.

The pain had begun suddenly while he was wrestling with a younger associate at about 7 p.m. This was at the end of a day of considerable exertion for one who had been leading a rather sedentary life as the patient had. He had hurriedly driven some 300 miles during the morning in order to arrive in time for the club picnic on the beach. He had bolted a lunch of pickles and sandwiches at home and had drunk several bottles of beer during the afternoon. He had played a game of beach baseball and had done a good deal of swimming before he

undertook the wrestling during which the pain struck him. He had not partaken of an evening meal.

He was rushed to the emergency room of the hospital within half an hour after the onset of the pain. In the emergency room he thrashed around a great deal, struggling, he said, for air.

He was lying flat on the carrier but pillowng him up did not seem to relieve him. There was a flushed red color with no definite cyanosis to be seen in the facies. The neck veins were not engorged. The physical examination of the heart revealed nothing pathognomonic of disease. The heart was not definitely enlarged but the rate was 110 per minute. The heart sounds were quite distant. No murmurs were heard. The blood pressure was systolic 140, diastolic 110 mm Hg. No rales were heard in the lungs.

The abdomen was considerably distended. There was tenderness in the epigastrium but no definite liver edge could be made out. There was no rigidity of the abdomen but some voluntary spasm was noted to be present. This gave way on careful deep pressure.

He was given a hypodermic injection of morphine $\frac{1}{4}$ gr (15 mg) and atropine 1/150 gr (0.50 mg) and this had to be repeated within half an hour. Electrocardiograms were taken within an hour after the onset of the attack, and showed an extremely high take off of the ST sector in Leads II and III with a slight downward deflection in Lead I (fig 1). It is most unusual to record such a high take off which may be considered evidence of a massive infarction of the posterior surface of the heart as a result of thrombosis of the posterior descending branch of the right coronary artery. The patient was unfortunately removed to the hospital when he could have been cared for just as well in bed in the electrocardiographic laboratory and the study of the development of the electrocardiographic changes could have been better carried out. Further significant and diagnostic laboratory data are tabulated in Table I and graphically shown in Chart I.

TREATMENT

After receiving $\frac{1}{2}$ gr (0.30 Gm) of morphine and 1/75 gr (0.01 Gm) of atropine in the emergency room he continued to complain of pain. He gradually became more comfortable in the hospital. His pulse rate remained at 110 per minute and his blood pressure had dropped to systolic 120, diastolic 95 at 9:30 p.m. and he was given his first dose of 50 cc of warm orange juice containing 15 cc of whiskey. This was repeated on the half hour when the patient was awake. His pulse rate rose to 120 and his blood pressure dropped to systolic 110, diastolic 92 at 10 p.m. During the night he had a slight recurrence of pain and was given another $\frac{1}{4}$ gr of morphine and 1/150 gr of atropine at 11 p.m.

He became considerably nauseated after this third injection of morphine and vomited a large amount of undigested food containing pickles which had been eaten twelve hours previously. His pulse rate was 120 and his blood pressure was systolic 114, diastolic 90 at midnight. At 3 a.m. the pain recurred and he was given 1/6 gr of morphine and 1/150 gr of atropine. He vomited again after this early morning injection of 1/6 gr of morphine. The vomitus was about the same in amount but this time contained some orange juice and fewer fragments of pickles. His blood pressure was recorded at systolic 120, diastolic 90 at 3 a.m. and systolic 130, diastolic 92 at 4:30 a.m. with the pulse rate of 110 and a fever

CORONARY THROMBOSIS AND CARDIAC INFARCTION

TABLE I

| Date | Blood Pressure | Tem- perature Fah. ^o | Leuko- cytes | % Fila | % Non F | Sedimentation Rate | Blood | | | Urine | | | | |
|--------|----------------|---------------------------------|--------------|--------|---------|--------------------|-------|------|------|-----------------|-----------------|-----------------|-----|------|
| | | | | | | | G | TNPN | BUN | Cr ₁ | Cr ₂ | Cr ₁ | | |
| 8-8-37 | 140/110 | 102 6 | 27,500 | 68% | 32% | 1 Hr - 30% | 133 | 50 | 33 3 | 1 3 | 4 7 | 2 | 0 5 | 5 0% |
| 8-9-37 | 114/80 | 103 6 | 30,800 | 68% | 32% | 1 Hr - 47% | 133 | 37 6 | 22 | 1 3 | 4 7 | 2 | 0 5 | 5 0% |
| 8-10 | 120/80 | 103 | 30 | 68% | 32% | 1 Hr - 48% | 111 | 50 | 24 | 1 3 | 3 3 | 2 | 0 5 | 5 0% |
| 8-11 | 100/70 | 103 | 43,300 | 64% | 36% | | 146 | 50 | 21 5 | 1 2 | 3 4 | 2 | 0 8 | 4 5% |
| 8-12 | 110/76 | 103 | 37,400 | 58% | 42% | | 100 | 66 | 24 | 1 7 | 4 1 | 1 5 | 5 | 7 0% |
| 8-13 | 104/72 | 102 | 37,400 | 63% | 37% | | 122 | 70 | 25 | 1 5 | 4 9 | 1 5 | 7 | 5 5% |
| 8-14 | 100/68 | 101 4 | 31,400 | 64% | 36% | 40 Min.-50% | 128 | 70 | 27 | 1 25 | 3 75 | 1 5 | 25 | 3 0% |
| 8-15 | 100/68 | 101 | 36,800 | 62% | 38% | 20 Min.-50% | 125 | 56 | 21 7 | 1 6 | 3 0 | 1 1 | 6 | 4 5% |
| 8-17 | 98/68 | 101 2 | 18,400 | 77% | 23% | 30 Min.-50% | 125 | 60 | 27 3 | 1 5 | 3 3 | 9 | 1 | 3 0% |
| 8-19 | 98/58 | 100 | 16,900 | 66% | 34% | | 122 | 66 | 30 | 1 4 | 2 7 | 7 | 3 | 2 0% |
| 8-20 | 98/66 | 98 6 | 13,800 | 67% | 33% | 40 Min.-45% | 105 | 100 | 27 5 | 1 2 | 4 0 | 1 5 | 5 | 3 5% |
| 8-22 | 108/70 | 98 6 | 15,600 | 75% | 25% | 40 Min.-40% | 105 | 60 | 27 3 | 1 5 | 3 3 | 9 | 1 | 3 0% |
| 8-26 | 104/80 | 98 6 | 15,050 | 80% | 20% | | 122 | 66 | 30 | 1 4 | 2 7 | 7 | 3 | 2 0% |
| 8-27 | 98 6 | 13,100 | 72% | 28% | | | | | | | | | | 2 0% |
| 8-29 | 108/70 | 98 6 | 10,900 | 86% | 14% | 50 Min.-20% | 105 | 44 0 | 27 | 1 3 | 4 7 | 1 3 | 5 | 5% |
| 8-31 | 120/80 | 98 6 | 9,910 | 85% | 15% | Chol-270 | 100 | 54 5 | 25 | 1 4 | 2 0 | 1 1 | 8 | 0% |
| 9-5 | 130/92 | 98 6 | 9,250 | | | | 98 | 49 0 | 25 | 1 2 | 3 5 | | | |

Table of Clinical and Laboratory Data on patient F A B for four weeks following an acute attack of coronary thrombosis with extensive myocardial infarction. G=Gluco TNPN=Total Non-Protein Nitrogen BUN=Urea Nitrogen Cr₁=Creatine Cr₂=Total Creatinine S=Sugar

of 101°. At 8:30 a.m. his blood pressure was systolic 128, diastolic 90, his pulse rate was 90 and fever 99.4°.

The p.r.n. order for morphine was changed to one for Dilaudid 1/32 gr. p.r.n. and two injections of the latter were given before the completion of the first twenty-four hours of his illness, one at 10:30 a.m. and one at 4:30 p.m., August 9, 1936. He had no further vomiting after this. The blood pressure dropped to systolic 114, diastolic 80 at 1:30 p.m. with a pulse of 88 and rose at 7:30 p.m. to systolic 120, diastolic 84 with a pulse of 96 and fever of 102.2°.

Besides the whiskey and fruit juice given during the night, barley water, clear broth and glycocoll 10 Gm., were given every four hours, turpentine enemas, a rectal tube and a small low rectal enema of glycerin were used to combat the disturbing distention. Dilaudid was given four times during the second twenty-four hours, August 10, 1936, during which the blood pressure remained at systolic 120, diastolic 80, but the pulse rose to 110 and the temperature to 103.4°. During the third twenty-four hours, August 11, 1936, Dilaudid was needed twice and the blood pressure dropped to systolic 100, diastolic 70, pulse 98 and temperature 103°. Each twenty-four hours for the next seven days Dilaudid 1/64 gr. (601 Gm.) was used to quiet him at night. He was given during the first ten days only fruit juices, barley water, and soups and 10 Gm. of glycocoll every four hours. Aminophyllin was withheld, in fact it was not given until August 20, 1936.

Further historical data on the patient were obtained as the patient recovered.

In retrospective study of this patient's case history, it was learned that about a week before this hospitalizing attack he had lifted a sack of beans in the course of his work and following this he had a pain in his back for two or three days. Furthermore he had been playing golf strenuously and enthusiastically for some weeks past. In the week before admission he had broken 80 and had gotten considerably excited about it.

Two weeks preceding this attack while playing golf he had a choking sensation and gripping pain in the midsternum which lasted only for a few minutes and disappeared on rest. At this time he had eaten his lunch very hastily and hurried out to the golf links and he therefore attributed his trouble to indigestion. Four weeks previous to this attack he had had similar symptoms that had lasted an hour or so after eating the evening meal. He went to bed early and dropped off to sleep and awakened feeling refreshed and well.

He admitted that he had been an excitable and worrisome type of individual and a very heavy cigarette smoker, consuming as much as two packages of Pieayunes a day. He had used alcoholic beverages steadily in the form of whiskey for two years past. About two years before admission he had taken up golf because he thought he needed exercise to overcome a general tired feeling and lack of energy. At about the same time, in 1934, while in Corpus Christi he had continued to feel below par and consulted a physician who had him under observation for two weeks. A diagnosis of sinusitis and tonsillitis was made and his tonsils were removed. He had his blood pressure taken at this time and the year previous to this, that was three years back, and it was each time reported normal. He had had an appendectomy performed in 1931 and shortly after this he had some sharp pains in the back that were considered to be due to kidney stones. The last life insurance examination that he had passed was in 1929.

He had had the ordinary diseases of childhood without complications.

His marital history was negative. He had been married for nineteen years and his wife had never become pregnant.

His family history was irrelevant. His father had died at an early age of what was thought to be tuberculosis. His mother had died of an unknown cause at an early age. Two sisters were alive and well and one brother was considered to be in good health. There was no family history of heart disease or vascular disease of any kind.

COMMENTS

This case record presents many interesting features which are worthy of further consideration. In the matter of immediate etiological diagnosis it seems quite likely that unduly strenuous exertion precipitated the attack. The anatomical diagnosis of acute coronary thrombosis with cardiac infarction seemed most likely but traumatic rupture of an aortic valve or of the aortic wall with the development of a dissecting aneurysm and acute distention of a saccular aneurysm as a result of blood pressure increase or trauma had to be considered in the differential diagnosis.

The blood pressure drop had not been precipitate. The diastolic blood pressure was fairly well sustained and there was no vascular throbbing such as one would expect in the presence of aortic valve rupture. The absence of a diastolic murmur and the Corrigan pulse as well as the low diastolic blood pressure constituted evidence against the rare traumatic rupture of the aortic valve cusp.

There was no radiation of pain to the leg as so characteristically occurs in dissecting aneurysm. No abnormal aortic dullness, pulsations or shocks were present to support a diagnosis of saccular aneurysm. There were thus no signs whatsoever to substantiate the diagnosis of an acutely distended saccular aneurysm of the aorta. These considerations along with the very characteristic electrocardiographic findings of myocardial infarction were considered sufficient to rule out ruptured aortic valves, dissecting and distended saccular aneurysm.

THE ELECTROCARDIOGRAMS

The electrocardiograms as shown in figure 1 with slight downward deflection and convexity of the ST sector in Lead I but extraordinarily high takeoff with sharp upward convexity of the ST sector in Leads II and III. The striking picture approaching a monophasic type of curve was considered to be the result of massive infarction.

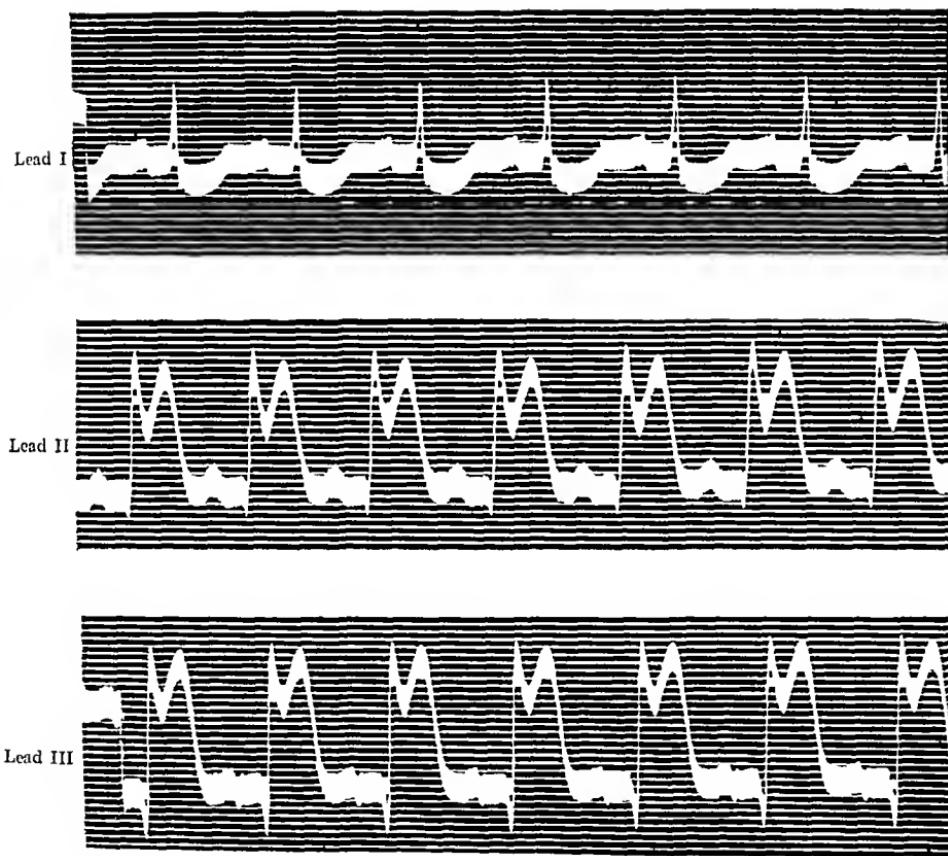
The changes in Leads II and III indicate that the posterior surface of the heart in the distribution of the right coronary artery was chiefly involved. These tracings were of course taken within an hour of the onset of the attack. The Q wave was evident in Lead II and already measured 0.7 m v in Lead III. The P R interval was prolonged to 20 of a second. It is indeed unfortunate that the patient was not kept in the heart station and electrocardiograms taken throughout the night so that the loss of R waves in Leads II and III and the development of Q2 and Q3 could have been traced.

The heat and humidity were such that the great difficulty of induction interference was experienced in getting curves with the Victor portable cardiograph in the old hospital building. The 60 cycle alternating induction current prevented our recording of further electrocardiograms until eighteen hours after the attack. At this time (fig 2) in spite of induction distortion it could be seen that the ST sector of Lead I showed only one mm depression of the takeoff, while in Leads II and III the ST sectors were only 2.5 and 3 mm above the isoelectric line. Q2 had become more prominent measuring 0.4 m v and was definitely slurred. Q3 had strikingly developed and measured 1.2 m v. The curves (fig 2) taken at 24, 36, 48, 60 and 108 hours showed relatively little changes from those recorded eighteen hours after the attack.

Again there was a lapse in the taking of electrocardiograms and during the interval of twelve days important changes again took place as figure 3 clearly demonstrates. The ST sector in Lead I had become almost normal and there was only a very slight downward curvature of the sector and T1 was upright. In Leads II and III the high takeoff had come down to within a millimeter of the isoelectric line. The upward convexity was still present but prominent T waves, T2 and T3, with rounded apices had developed. There was some slurring of the Q2 which still measured 0.4 m v. Q3 measured 1.4 m v. The P R interval was now short, 12 to 14 of a second. The tracings made on August 31, September 20, October 15, and November 15, 1936, and January 12, 1937, showed practically no changes.

There have not yet accumulated enough serially taken electrocardiographic data upon which to base any conclusions as to the prognostic significance of the time of appearance and disappearance of the characteristic changes. It may be that the rate at which the ST sector

FIG 1



Electrocardiograms taken within one hour of the onset of pain in patient F A B Leads I, II and III from above down note the striking and characteristic depression of ST_1 with downward convexity and the unusually high takeoffs of ST_2 and ST_3 with high T_2 and T_3 Q_2 is present and Q_3 measures 0.7 millivolts

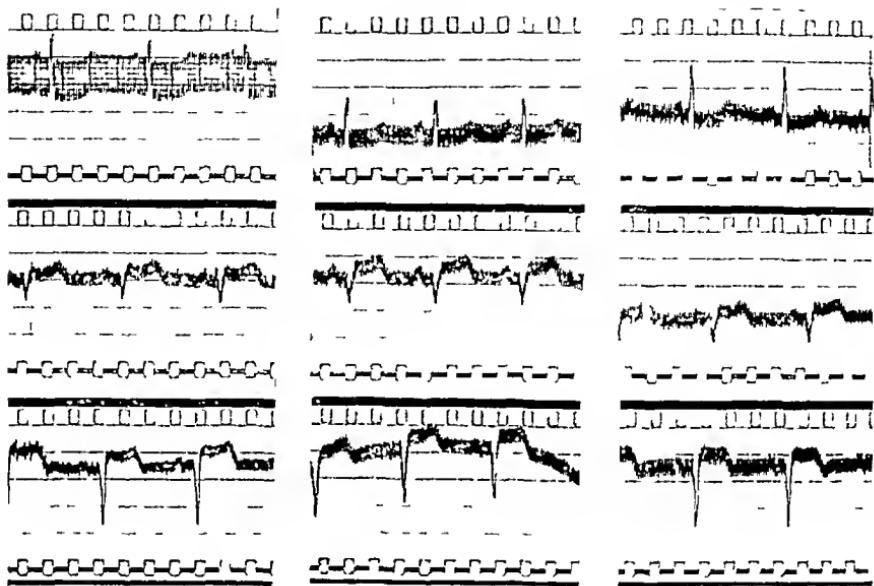
FIG 2

18 Hrs

24 Hrs

30 Hrs

Lead I



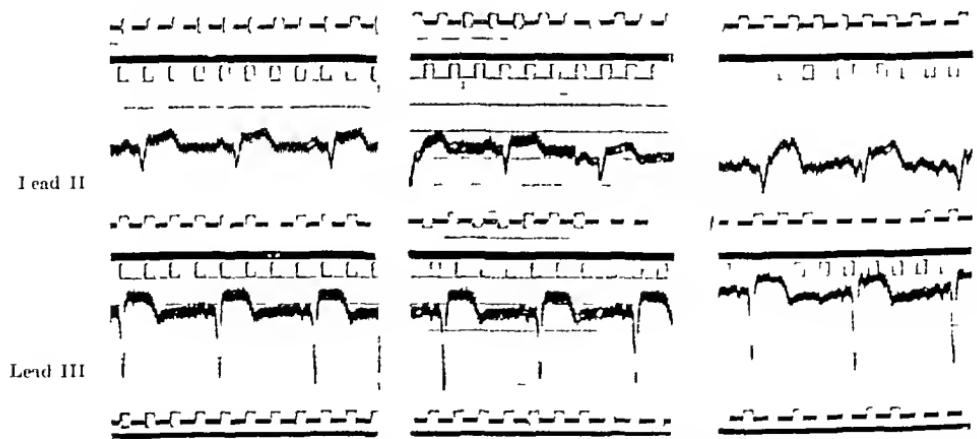
Lead II

48 Hrs

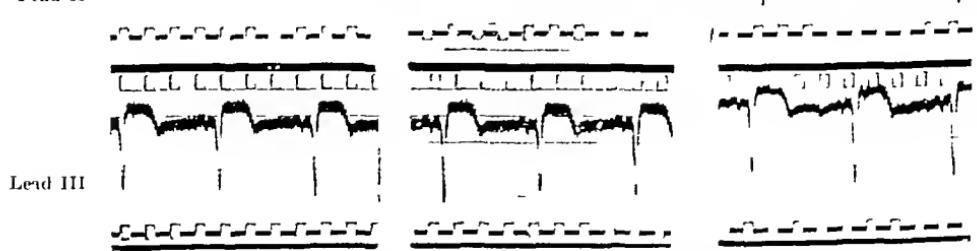
60 Hrs

108 Hrs

Lead I



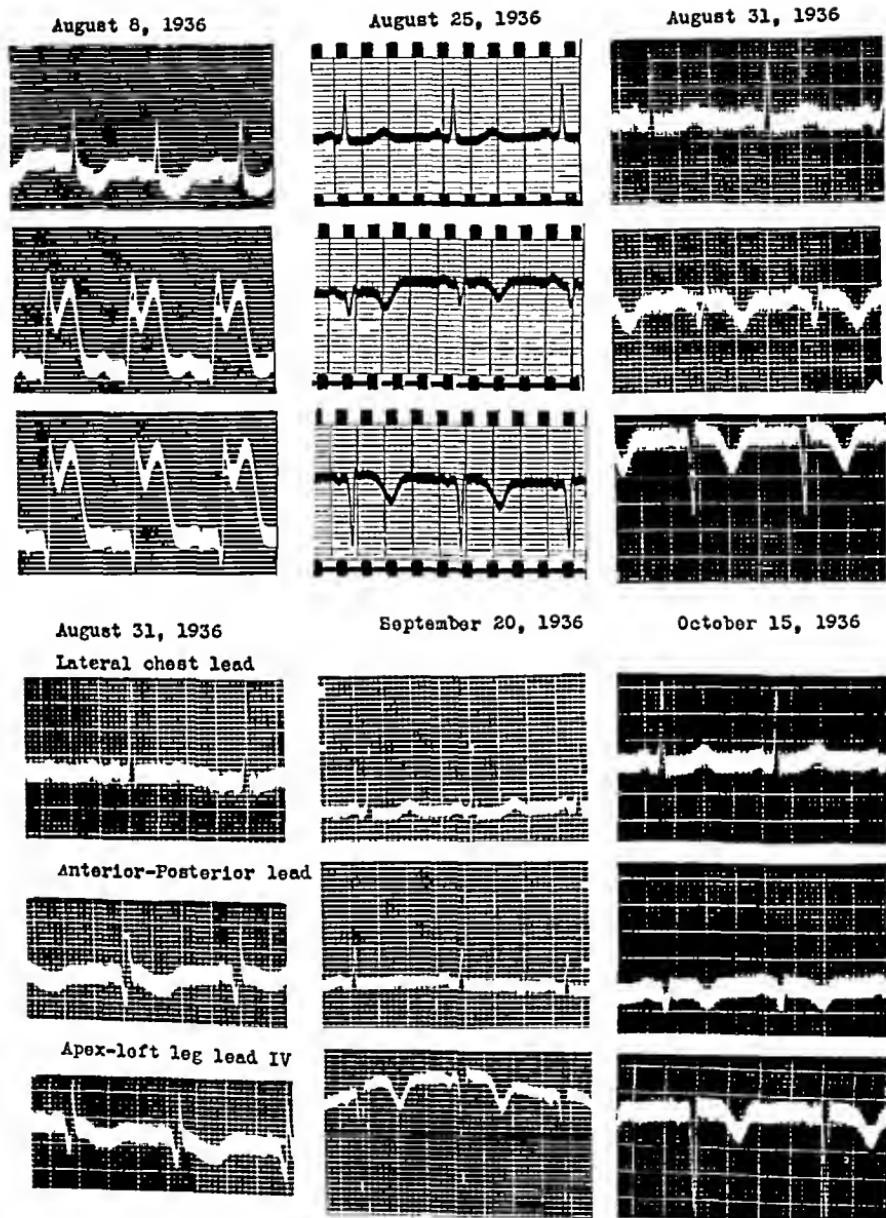
Lead II



Lead III

Electrocardiograms of patient F A. B taken on the Victor Portable Instrument at 18, 24, 36, 48, 60 and 108 hours showing the rather rapid development of Q and Q₂ and the rise to the baseline of ST₁ and the more gradual falls of ST₂ and ST₃ with the development of convexity upward and the sharp negativity of T₃.

FIG 3



Interval electrocardiograms on patient F A B showing the developed and slurred Q and Q₃ and the sharply negative T₂ and T₃ and the persistence of these abnormalities

FIG 4

3/17/35

3/21

4/17

5/27

7/21

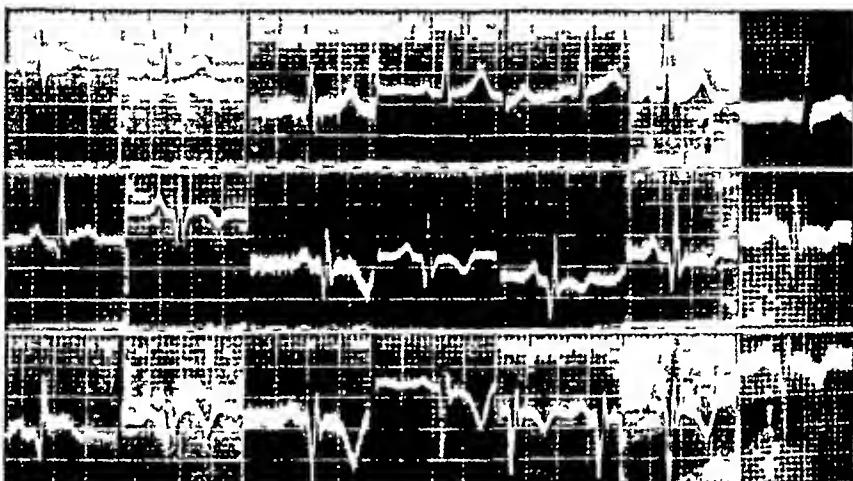
9/20

10/20

Lead I

Lead II

Lead III



Electrocardiograms on T. C. L. at intervals of days and months showing a more gradual development of the characteristic exaggerated Q_2 and Q_3 and T_2 and T_3 with slight recession of the sharply negative T_1 and T_3 .

elevation and subsequent descent and T wave negativity develop are of significance. This may be a source of prognostic information worthy of further investigation.

All electrocardiograms recorded on our patient after the original one (fig 1) showed the very prominent downward deflections in Lead III which might have been considered as S waves had not the original curves been taken. The latter substantiate the opinion that the chief downward deflections in Leads II and III are Q waves and not S waves. Without the original curves then, one would have a tendency to make a diagnosis of left axis deviation, or left ventricular predominance or actually left ventricular preponderance. The evidence at hand is certainly against the last opinion though it is conceivable that infarction of the right ventricular muscle mass might give rise to left sided electrical predominance or axis deviation.

Progressive changes in repeated electrocardiograms constitute the strongest evidence that we can have in the diagnosis of cardiac infarction of coronary thrombosis origin with progressive changes in the ventricular myocardium. The importance of serial electrocardiograms cannot be overemphasized. The failure in this case to follow up the original curves immediately with frequent tracings throughout the night was a serious error of omission, the missing of an unusual opportunity that presents itself only once in a great while.

PROGNOSIS

The electrocardiographic evidence presented is confirmative, I believe, of the clinical impression that the patient had a massive cardiac infarction. The *localization* of the process to the posterior surface of the heart seems to give the patient a more hopeful outlook. Patients with electrocardiograms of the Q3 and T3 type seem to have a better prognosis. I have had two other patients recently, one a young man about this patient's age and another slightly older, both of whom survived extremely severe episodes of posterior myocardial infarction and have been fairly well rehabilitated. In one of these cases the development of the Q2 and Q3 waves (fig 4) was similar to that of our present case but more gradual. The clinical impression is thus further supported that patients presenting the electrocardiographic changes only in Leads II and III, that is the results of a right

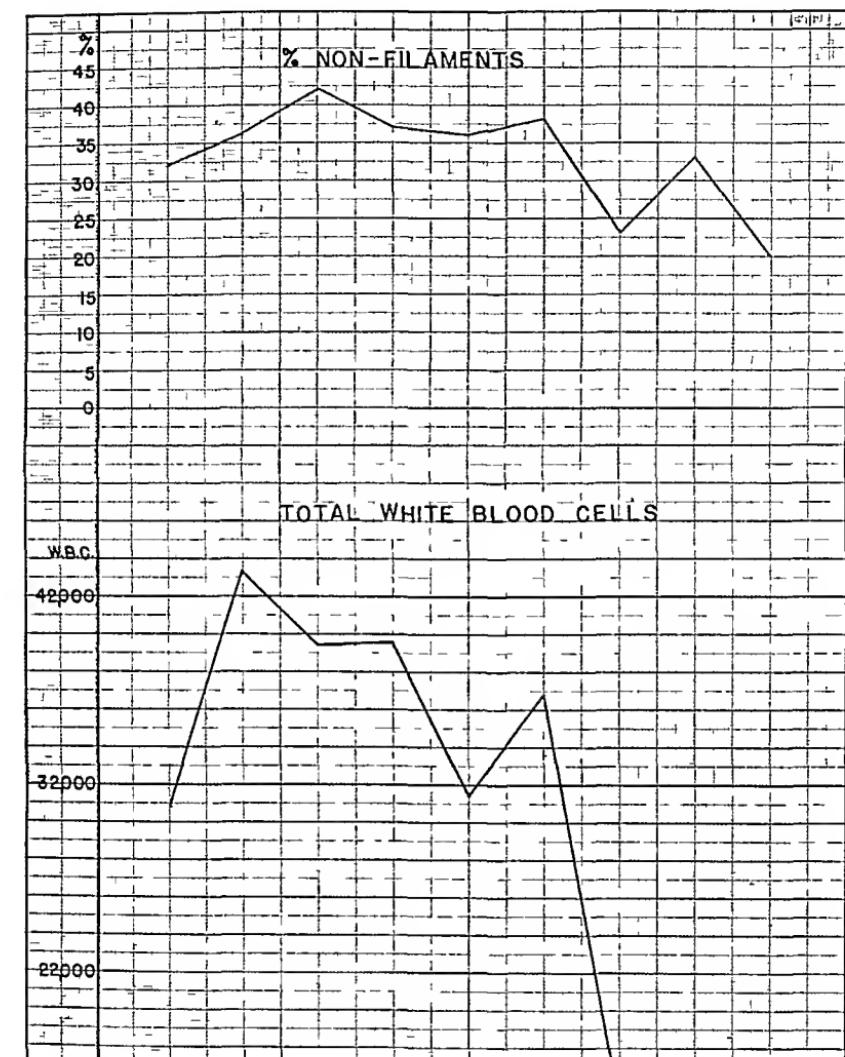
coronary artery lesion, have a better outlook than those that present similarly striking changes in Leads I and II

Severity and the persistence of the pain, the height of the temperature rise, the long persistence of the febrile state, drops in the blood pressure to low levels and its remaining there are all facts, which would forbode an unfavorable outcome. These were all present in our case and yet the patient survived. Furthermore, there were present in addition other ill omens, namely the high *leukocytosis*, of 43,000, the high percentage of *nonfilamented forms* usually above 30 per cent and occasionally as high as 45 per cent, and a striking increase in the sedimentation rate which persisted for twenty days might well be cited as signs against recovery. It might be said, however, that in this patient the *sedimentation rate* increase was progressive over a period of days and did not reach its maximum until late. In the differential blood count the eosinophiles were then also considerably increased.

The studies of Goodrich and Smith and others have made a good beginning in the determining of the prognostic significance of laboratory data yet it is apparent that we need a great many more observations before we can establish our normal limit or rather our favorable limit for these laboratory data and know when they are definitely favorable. Another recent case comes to mind, that of an elderly woman in whom the leukocyte count and the proportion of nonfilamented forms were in the unfavorable limits and in whom on one occasion for no known reason, the blood picture showed a striking erythroblastosis, yet the patient recovered completely and is carrying on with slight limitation of her activities.

The *blood chemical changes* are of considerable interest. In the first place I must mention the *hypercholesterolemia* with the cholesterol levels of 280 mg per cent. I mention this particularly because in another recent case of coronary thrombosis in a young man whose curves are shown in figure 4, a hypercholesterolemia of 500 mg per cent persisted even after the other blood chemical changes became normal. This is evidence of a serious metabolic disorder. These patients may have had a mild hypothyroidism or a mild diabetes mellitus. At any rate it raises the question what part hypercholesterolemia plays in the atheromatous changes in the coronary arteries of these young men. We feel that the hypercholesterolemia

FIG 5



contributes to the atheromatous vascular degeneration of chronic diabetes mellitus cases. We know relatively little about the vascular changes of chronic hypothyroidism.

Our present patient, as well as the other young man mentioned, showed a glucosuria and a hyperglycemia of 183 mg per cent and considerable retention of nitrogen waste products with a nonprotein nitrogen of 50 mg per cent. Urea nitrogen of 33.3 mg per cent and a total blood creatinine of 6 mg per cent and a creatine of 1.3 to 2.6 mg per cent and a constant creatinuria of slight grade (See Table 1). Such blood chemical changes are common in patients who suffer from coronary thrombosis (See Chart 4). It is of course impossible to say what these patients had preceding the attack but the fact that there was some fluctuating drops and secondary rises and then a gradual drop from the abnormal values toward the normal levels as recovery progressed suggests that the blood chemical changes were the result of the pathological physiology of cardiac infarction. The causes of the fluctuations during the course of the acute illness are not certain but it seems quite likely that these changes may well have been associated with circulatory upsets that resulted from the dynamic disturbances of acute cardiac infarction. It is possible that some of the changes were produced by the disintegration of the heart muscle in the infarcted area.

THE CHEMISTRY OF THE HEART MUSCLE

In considering the blood and urine chemical changes in this case it might be worth while to cite some of the findings encountered upon microchemical analysis of the infarcted muscle contrasted to that from uninfarcted areas in human hearts (Table 2). The conspicuous loss of creatine from the infarcted areas may be quite significant.

TABLE II

Creatine Values in Human Heart Muscle after Coronary Occlusion

| Height | Weight | Creatine (mg %) | | Solids (%) | | Dried (mg %) | |
|---------------|--------|-----------------|-----------|------------|-----------|--------------|-----------|
| | | Good | Infarcted | Good | Infarcted | Good | Infarcted |
| 610 | | 122 | 41 | 23.45 | 18.0 | 520 | 228 |
| 350 | | 104 | 61 | 21.95 | 15.05 | 497 | 405 |
| 800 | | 100 | 52 | 19.7 | 18.2 | 558 | 318 |
| 900 | | 151 | 31 | 19.15 | 17.25 | 788 | 180 |
| normal values | | 175 + | - 20.7 | 20.3 + | - 0.87 | 868 + | - 70 |

Chart 2 was made up of the results of a series of the chemical analysis of the dogs' heart muscle from experimentally infarcted areas as contrasted to the data from uninfarcted areas. In these dogs' hearts usually the anterior descending branches of the left coronary arteries had been experimentally tied and the animals sacrificed at various

FIG. 6

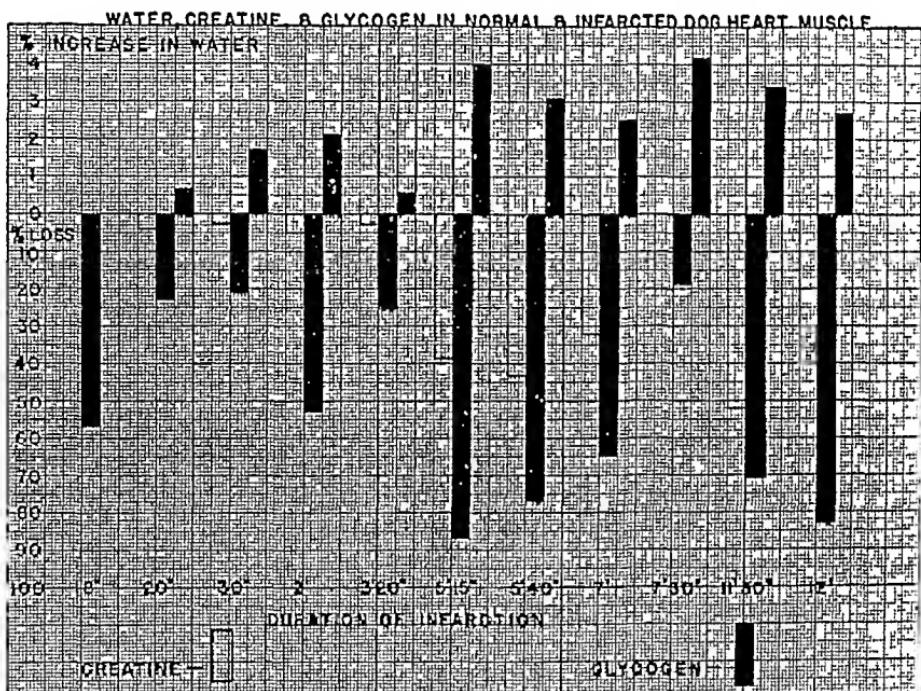


Chart 2 showing the losses of creatine and glycogen from experimentally infarcted areas of dogs' hearts analysed at minutes 18, 20, 30 and hours 2, 3½, 5¼, 7 ½, 11½ and 12 after ligation of anterior descending branches of the coronary arteries. The gains in water content or edema are indicated in the columns above the zero line. Note that the creatine and glycogen losses and edema are greatest at about the fifth hour after interruption of the coronary circulation.

intervals. It is to be seen that there was a very sharp drop in the glycogen content of the infarcted muscles shortly after interruption of the circulation. After about five hours the loss of creatine became evident and increased some for some hours and continued for at least twelve hours. The creatine losses are not as soon to appear nor as striking as the glycogen losses but they are perhaps just as significant. With these losses, the chemical constituents of importance in muscular contraction are dissipated, and there is simultaneously an increase in the water content of the heart muscle. Charts 3 and 4 show some

creatine and creatinine changes in experimental and clinical coronary thrombosis

TREATMENT

We have noted creatine losses in human hearts from patients who have died in congestive failure and in isolated animal hearts that have

Fig. 7

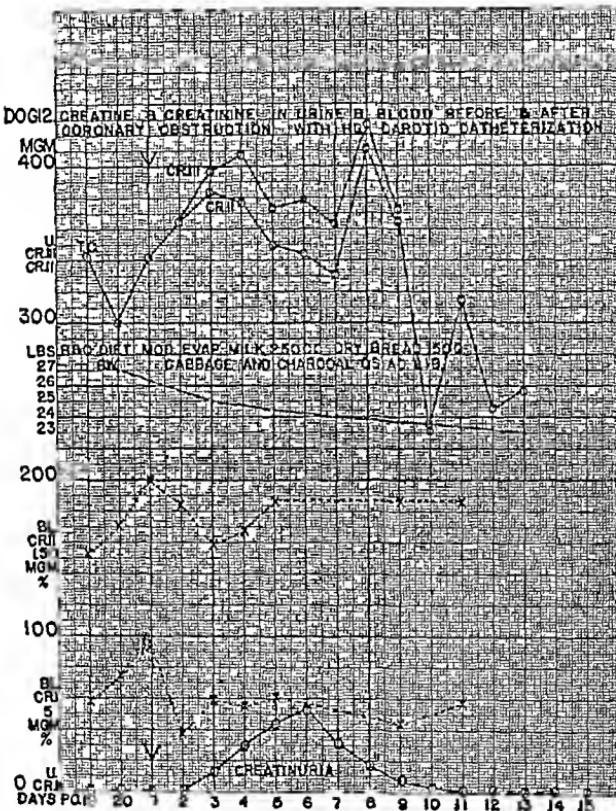


Chart 3 showing the blood and urine creatine changes in dog 12 in which the coronary artery was obstructed by mercury introduced through the carotid artery by a canula which was carried down into an anterior aortic sinus

been driven to failure. In an attempt to find possible precursors in aminoacids and in order to stem the tide of the disappearance of the essential creatine we have perfused isolated animal hearts with solutions of various aminoacids. Alanine and glycocoll alone of all the aminoacids seemed to prevent the great losses of creatine. The reason for this may be the specific dynamic cellular stimulating effect of

these aminoacids but there is no proof that such is the case. At any rate the results of the perfusion studies encouraged us to use glycocoll or glycine in patients with myocardial insufficiency and in those who have suffered acute coronary thrombosis. Whether or not the use of aminoacids is of any value under such circumstances I am not prepared to say. It is difficult to get proof in the matter of therapeutic value of such a preparation. There is no apparent danger in the use of glycocoll as a food substance except that as such it is a rather costly

FIG. 8

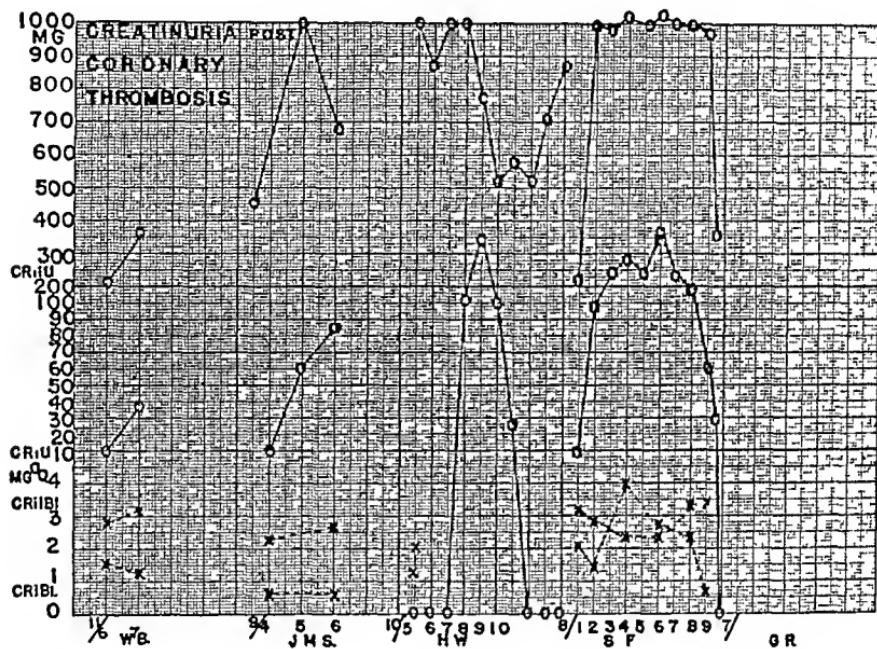


Chart 4 Blood and urine creatine changes in four patients following coronary thrombosis. CRiU = Creatine in urine CRiB = Total creatinine in U CRiB = Creatine in blood CRiB = Total creatinine in blood Creatinuria and creatinemia are abnormal but not specific or pathognomonic. The administration of drugs particularly ammophyllin interfere with creatine studies

substitute. I have used glycocoll in several cases of what appeared to be severe infarctions, as this case did, and the outcome has been favorable. I do not know that the use of glycocoll had anything to do with the happy results. I believe, however, that it is worthy of further trial as a supportive therapeutic agent. Gelatin may be used as a substitute because of its high glycocoll content.

The chief therapeutic indication in coronary thrombosis attacks is the relief of the pain as promptly and as completely as possible. Morphine sulphate should be administered in half grain doses at the onset

but when it is found that morphine nauseates the patient and causes him to retch and vomit some other narcotic should be tried. Dilaudid in doses of 1/32 gr (0.002 Gm) instead of 1/4 gr (0.015 Gm) of morphine is often preferable because of less gastro-intestinal disturbing effect. This was observed in the treatment of the subject of this discussion. Pantopon in 1/6 gr (0.01 Gm) doses alone or with papaverine hydrochloride 1/3 gr (0.02 Gm) and Atrinal (atropine sulphuric acid ester) 1/60 gr (0.001 Gm) as combined in Roche's "Spasmalgin" may be used to advantage. Relief of pain, rest and relaxation must be obtained at any price within reason. In rare instances alcoholic injection or extirpation of the upper thoracic sympathetic ganglia may be necessary.

One of the chief therapeutic contraindications is the use of ephedrine hydrochloride or sulphate in an attempt to bolster up a falling blood pressure and a failing myocardium. Ephedrine has a tendency to produce serious mechanism disorders, particularly paroxysmal ventricular tachycardia. Of course the disorder usually responds to the ingestion of quinidine sulphate in 5 gr (0.3 Gm) doses every hour for not more than eight doses. If the patient is vomiting the quinidine may be given by rectum and is usually equally effective. Some cardiologists give quinidine routinely to prevent the spontaneous appearance of ventricular tachycardia. I am prone to hesitate in using quinidine until it is definitely indicated for the appearance of atrioventricular or intraventricular condition disturbances contraindicate the use of quinidine. As long as the blood pressure is in the neighborhood of systolic 80 and diastolic 60 nothing need be done but if it falls below 70 mm Hg and unconsciousness and loss of sphincter control intervene, something must be done to save the patient. Under such conditions adrenalin in small doses (0.5 cc, 1:1000 sol) is perhaps the drug of choice and must be repeated at hourly intervals. Coramine in 1 cc of 10 per cent solution given intramuscularly every hour may be as effective and less dangerous. Such regimes have tided a patient over a critical period of hypotension to recovery.

In acute heart failure, *venesection* is in order and may be a life saving procedure. When the failure is chiefly left ventricular with acute edema of the lungs the withdrawal of blood does very little good. In such instances large doses of *atropine* 1/75 to 1/50 gr

(0008 Gm to 0013 Gm) should be added to the narcotic which is always to be given Intravenous cardiac tonics as ouabain and strophanthin even in 1/240 gr (00025 Gm) doses are not without danger *Digalen* in sufficient dosage intramuscularly to be effective may be likewise dangerous *Oxygen therapy* if available in a tent or room is the best possible therapy for deeply cyanosed patients and those with pulmonary edema I have seen one physician survive an attack in which he had to be kept in an oxygen tent for a week

The combating of pulmonary edema by intravenous injection of 50 per cent glucose solution or sucrose or sorbital may be effective but may put a considerable strain upon the circulation by a temporary increase of the blood volume The glucose, too, should not be given if the patient already has a post coronary thrombosis hyperglycemia In the presence of the latter it should be remembered that such patients tolerate the injection of insulin poorly for the sudden drop of the blood sugar that is likely to result in the hypoglycemia would play havoc with the already impoverished heart muscle If the diabetic state is threatening then small doses of a slower acting insulin as protamine zinc insulin may be tried with great care and only in cases in which blood sugar determinations can be frequently made

SUBSEQUENT MANAGEMENT

After the patient has survived the shock of acute cardiac infarction and his restlessness has been controlled, he must be continued at complete rest in bed and not even allowed to feed himself or change his position for fear that the strain will cause a rupture of the necrotic myocardium He should be continued on a liquid diet to which *whiskey* may be added for its caloric value and its vasodilating effect Fruit juices and sugar are administered frequently if they do not produce distention If there is a glycosuria or hyperglycemia present barley water or thin oatmeal gruel with or without *glycocoll* may be given every hour in small amounts throughout the day

In cases in whom creatine studies are not going to be made the patients may be treated from the beginning with aminophyllin, 1½ gr (0.1 Gm) doses completely dissolved in water every three hours for six or eight doses Intolerance to aminophyllin by mouth may necessitate rectal or even intravenous administration for the relief of

pain. The occurrence of premature ventricular contractions with any degree of frequency should be considered an indication for quinidin, 3 to 5 gr (0.2 to 0.4 Gm) every three hours as a prophylactic against attacks of acute paroxysmal ventricular tachycardia. Quinidin may also prevent the development of the usually fatal ventricular fibrillation into which the ventricular tachycardia may easily change or go over. Quinidin should be withheld if the electrocardiograms show any evidence of impaired A-V or I-V conduction.

When heart block has been produced and fainting attacks recur it may be necessary to give the patient small doses of *adrenalin* at regular intervals to ward off the fatal syncope. Auricular fibrillation only occasionally has been precipitated by coronary thrombosis. In such cases *cinchonization* should first be tried in the hope of restoring normal mechanism. If this is unsuccessful and the pulsus deficit is of any significance digitalization must be resorted to in spite of the presence of coronary thrombosis.

A metabolic disturbance such as diabetes mellitus calls for dietary management and control without the use of insulin if the case is not too severe or one of total aninsulinism. Hypothyroidism or any such intercurrent disorder, the treatment of which might interfere with the recovery from acute myocardial infarction, must await recovery from the acute episode before treatment is given even though the condition may have contributed to the vascular damage. During the first few days after the survival from the initial shock one must try to prevent, by absolute rest, such complications as cardiac mechanism disorders, rupture of the heart through the infarcted myocardial area, advancing thrombosis or the appearance of a secondary thrombus formation in another branch of a coronary artery and embolism. Passive change of position, however, must be carried out, for in some instances the hypostatic congestion of the lungs may lead to pneumonia. Low blood pressure may furthermore impair the circulation through the kidney and result in the accumulation of nitrogenous waste products, poor renal function and uremia. Each day of survival after the attack removes the patient a bit further from the dangers of these complications. After the first week or ten days have passed the chances of recovery are distinctly better.

The diet must, however, continue to be of a semiliquid, soft nutritious fairly concentrated type and be given in frequent feedings.

The main point is that the feedings should be small and the work of digestion should be kept at a minimum. Masters has advocated a low caloric diet of about 500 to 800 calories which may have some advantages.

After three weeks of complete bed rest the patient may be allowed more activity in bed but he certainly should remain there for another three weeks if it is economically possible to do so. After six weeks' rest in bed the infarct may be considered healed, particularly so if the erythrocyte sedimentation rate has returned to normal. There is unfortunately no way of determining whether endocardial mural thrombosis from which an embolism may arise is present or not.

Massage and passive exercises may be carried out in bed and the patient allowed gradually to sit higher and higher each day after the third week. At the end of the sixth week the patient's feet may be put over the side of the bed for longer and longer periods of time, increasing an hour each day. Then the patient may be gotten up and allowed to sit in a chair but only after a week or ten days may he assume the upright standing position. He must be permitted to walk only a few steps at first along the bed and then day by day around the room. He must be warned not to change positions suddenly. The rehabilitation to the point of return to his activities requires a month or more.

During the first few weeks a bed pan must be used and after the sixth week a commode at the side of the bed is desirable. Bathroom privileges can be given only after the patient is up and around and he must be constantly advised not to strain at stool.

In most patients it is desirable to continue medication of *vasodilating* drugs. In this category theophyllin preparations, theophyllin ethylene diamine or theophyllin glucamine in 3 or 4 gr (0.2 to 0.3 Gm.) doses completely dissolved in water three times a day are most effective. Theophyllines assure the maximum coronary circulation and usually relieve the light minor but aggravating precordial pains that often recur from time to time after thrombosis. Some individuals who cannot take the drug by mouth may take it in a suppository by rectum and I have one patient who insists on having it intravenously every time he has a recurrence of precordial distress. In a large proportion of patients who survive attacks of cardiac infar-

tion some pain is experienced particularly by individuals who had never had it before the accident

A continuation of low caloric intake is particularly desirable in those who are overweight. Carbohydrate restriction must be carried out in those who have a tendency to diabetes mellitus. An adequate carbohydrate intake and even a high carbohydrate diet have been advocated. Disturbing gastro-intestinal distention may persist and call for modification in the dietary. In some cases the vitamin B1 intake has been greatly restricted and the body supply depleted and the administration of the same may increase satisfactorily the gastro-intestinal tone. In those patients with spastic conditions in the descendens and sigmoid belladonna, atropine, novatropine or syntropine may be used to advantage.

The patient may return to and gradually assume his normal occupation provided of course that he guards himself against sudden strain and provided that his occupation is a sedentary one as it fortunately frequently is in patients with this trouble. For those invalidated by coronary thrombosis who have done hard labor only in the past it is necessary to make some adjustment and have a social service worker attempt to get the patient into some occupation that requires a minimum of physical exertion. Former golf enthusiasts should be gotten interested in some sedentary game and hobby for it is just as well for them to give up golf as well as all other competitive athletics. Walking slowly on level ground for short distances at a time several times a day will usually provide adequate exercise. The use of tobacco should be forever prohibited.

THE FOLLOW-UP RECORD

The patient that we have under discussion was treated, handled, managed and advised along the lines that I have set forth. He survived and at the end of the third week his request to be moved to his home in an ambulance was granted. He remained in bed for three more weeks and then was gradually gotten up. After ten weeks he was permitted to be taken to his office in a motor car and on an elevator and remain at his desk a few hours each day.

He rather chafed at the restrictions imposed upon his activities and he felt that the limiting rules were too stringent. He therefore assumed more and more liberties until in his eleventh week he cut

short his night's rest in order to attend meetings and spent long hours on his feet. In his twelfth week he noticed an increasing pitting edema of his ankles and tenderness in his liver area and on one occasion had a slight choking sensation in his neck and in the floor of his mouth. This convinced him at the time that he must respect his physician's orders. He had gained ten pounds in weight.

Six months after his attack, after he had developed a good walking tolerance, he began, on his own initiative, to ascend ten steps at his office. He took only a half step at a time and counted ten on each elevation before proceeding to the next. He seemed to tolerate this satisfactorily in spite of the fact that he had gained five more pounds. Examination revealed some puffiness and stiffness of the hands and thinning of the eyebrows and sensitiveness to cold, apparently the result of hypothyroidism. His blood pressure had risen to systolic 150, diastolic 100 in his left brachial and systolic 142, diastolic 96 in the right brachial and his pulse rate was 90. After resting for ten minutes his systolic blood pressure dropped ten millimeters. Substitution therapy with thyroid extract will be withheld until the symptoms become much more troublesome for a low basal metabolic rate is desirable in a cardiac invalid. The further management will not vary much from what it has been except that sharp restrictions in his caloric intake will be urged upon him.

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THE SIGNIFICANCE OF CARDIAC MURMURS*

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Not many years ago cardiac murmurs were synonymous with valvular heart disease, a conception frequently resulting in serious harm to the patient, e g chronic invalidism, undue heart consciousness, and sometimes the refusal of a needed operation. Advances in physiology and pathology have changed this view so that today the significance of heart murmurs can be determined only by evaluating the condition of the coverings, muscle and valves of the heart, the mechanism of the circulation, the structural relationship of the heart to the other thoracic organs, and many other factors, in other words only by evaluating a thorough examination of the individual.

Both physician and patient should appreciate that today the efficiency of the cardiac muscle is of paramount importance and often has greater significance than the murmur in the diagnosis of cardiac disease. Many physicians still consider murmurs synonymous with heart disease, others find the interpretation of these sounds difficult. For these reasons a discussion of some of the cardiac murmurs is justified.

Heart murmurs are abnormal sounds produced by vibrations of tissues and not by the blood stream. These vibrations may arise in the pericardium, myocardium, heart valves, arteries or veins when they are rendered pathological by congenital defects, or by thickening, stiffening, constriction, contraction, dilatation or perforation of the affected part. Vibrations due to loss of muscle tone or to increased velocity of the blood flow produce the functional murmurs.

In studying cardiac patients the history is essential, and frequently will reveal valuable information for evaluating the significance of a murmur. Of equal importance is a complete physical examination, and there is no part of it which requires more attention to detail than the examination of the heart. Inspection, palpation,

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percussion, and auscultation should all be used routinely. Unfortunately, auscultation is frequently used alone, or is improperly or incompletely performed with attention given only to the murmur. Indeed some physicians use auscultation for the sole purpose of determining whether or not murmurs are present and thereby diagnosing or excluding heart disease. When such importance is given to murmurs it is but natural that serious diagnostic and prognostic errors are made. These mistakes have resulted from failure to appreciate that murmurs may be present without heart disease, e.g. murmurs with anemia, hyperthyroidism or exercise, and failure to recognize conversely that serious heart disease may be present without murmurs, e.g., coronary artery sclerosis and aneurysm of the aorta. Laboratory aids are sometimes invaluable and special blood, roentgen ray and electrocardiographic studies may be of great assistance in the proper interpretation of murmurs. The following brief case reports illustrate these statements.

CASE No 1—A male, sixteen years of age, consulted me with the chief complaint of weakness, dyspnea on exertion and palpitation. His physician had found cardiac murmurs and had diagnosed heart trouble. The history also revealed marked epigastric distress, aggravated by food and occurring directly after meals, with black tarry stools. Physical examination showed marked pallor and epigastric tenderness. There was no enlargement of the heart. Systolic murmurs were heard over the pulmonary, mitral and aortic areas. The blood count was Hemoglobin 43 per cent, red cells 2,944,000, leukocytes 9,375. Repeated examinations of the stools were positive for occult blood. Treatment for gastric ulcer and anemia was followed by complete recovery with the disappearance of all symptoms and the heart murmurs.

CASE No 2—A male fifty years of age consulted me with the chief complaints of dyspnea, precordial pain and palpitation. Another physician had diagnosed hypertensive heart disease because of a murmur and an elevated blood pressure. Additional evidence in the history revealed loss of weight, generalized throbbing of the vessels, excessive perspiration and tremor of the hands. Physical examination showed palpable thyroid, tremor of the hands, slight cardiac hypertrophy, forcible heart sounds, a systolic murmur at the mitral area with an apex rate of 120 beats per minute, and a blood pressure reading of systolic 100 mm., diastolic 70 mm. Examination of the urine revealed a slight trace of sugar. The metabolic rate was plus 46 per cent (Dubois) plus 50 per cent (Benedict). Following thyroidectomy the heart sounds became normal and murmurs were no longer heard.

CASE No 3—A female, twenty seven years of age, consulted me with the chief complaint of heart trouble. The history revealed recurrent attacks of precordial distress with pain along the left costal margin not related to exertion or emotion, of one year's duration. At the onset of the illness she consulted a physician, who, during the course of the examination, made her hop twenty-five

FIG 1



Ruptured aneurysm of the aorta. In this case no murmurs were heard

FIG 2



Acute bacterial endocarditis. Note large vegetations present. During the entire illness the murmur heard was very faint and at times so faint that it was not detected by some examiners.

times. Following this exercise he detected a heart murmur, told the patient that she had endocarditis, and advised a period of rest in bed for three months, which advice she followed. She continued to consult the physician from time to time for endocarditis. My examination failed to reveal enlargement of the heart and no murmurs were heard when the patient was quiet. Following exercise a systolic murmur was heard over the pulmonary area, transmitted down the left border of the sternum. This promptly disappeared with rest. Reassurance that the heart was normal and resumption of all activities was followed by complete recovery.

CASE NO. 4.—A male, forty-four years of age, was suddenly seized with a burning sensation beneath the lower sternum. It first appeared while he was climbing a steep grade after which it occurred each time he exerted himself and disappeared with rest. About one week later the discomfort came on after the evening meal following slight effort. During the night he awakened with the same sensation which persisted until morning. At that time a physician was called who found no abnormal signs referable to the heart or the blood pressure and because of this stated that no heart trouble was present. Five days later the patient consulted me. He described the above history which was typical of recurring angina pectoris followed by coronary occlusion. Physical examination of the heart failed to reveal any abnormal findings. However, the electrocardiogram showed an abnormal take off of the T wave in lead one with reciprocal changes in lead three, thus confirming the diagnosis. Following treatment he made an uneventful recovery and has remained well for three years.

CASE NO. 5.—A male, fifty-two years of age, was admitted to the University Hospital complaining of cough, dyspnea, and pain in the right chest of eighteen months' duration. The illness began with pain in the region of the right nipple which was associated with cough and shortness of breath. The pain and cough increased in severity until relief could only be obtained by sitting up in bed bending forward. Physical examination of the heart showed no enlargement. No murmurs were heard, the sounds being clear and distinct. The blood pressure was systolic 100 mm., diastolic 80 mm. A visible and palpable impulse was found at the second interspace to the right of the sternum with increased retro sternal dullness. A diagnosis of aneurysm of the aorta was made and confirmed by roentgenograms of the chest. At autopsy a ruptured aneurysm of the aorta was found (fig. 1).

Certain criteria should always be sought in studying murmurs:

- (1) The presence, or absence, and the quality of the heart sounds,
- (2) the location of the murmur, i.e. the area at which it is best heard, e.g. mitral, aortic, tricuspid or pulmonary,
- (3) the time of the murmur in the cardiac cycle,
- (4) the duration of the murmur,
- (5) the quality, the pitch, and the intensity of the murmur,
- (6) the transmission of the murmur,
- (7) the effect on the murmur of posture, respiration and exercise.

These criteria should be carefully and routinely determined. Each has its importance. First of all, it is essential to ignore the

FIG 2



Acute bacterial endocarditis. Note large vegetations present. During the entire illness the murmur heard was very faint and at times so faint that it was not detected by some examiners.

times. Following this exercise he detected a heart murmur, told the patient that she had endocarditis, and advised a period of rest in bed for three months, which advice she followed. She continued to consult the physician from time to time for endocarditis. My examination failed to reveal enlargement of the heart and no murmurs were heard when the patient was quiet. Following exercise a systolic murmur was heard over the pulmonary area, transmitted down the left border of the sternum. This promptly disappeared with rest. Reassurance that the heart was normal and resumption of all activities was followed by complete recovery.

CASE NO. 4.—A male, forty-four years of age, was suddenly seized with a burning sensation beneath the lower sternum. It first appeared while he was climbing a steep grade after which it occurred each time he exerted himself and disappeared with rest. About one week later the discomfort came on after the evening meal following slight effort. During the night he awakened with the same sensation which persisted until morning. At that time a physician was called who found no abnormal signs referable to the heart or the blood pressure and because of this stated that no heart trouble was present. Five days later the patient consulted me. He described the above history which was typical of recurring angina pectoris followed by coronary occlusion. Physical examination of the heart failed to reveal any abnormal findings. However, the electrocardiogram showed an abnormal take off of the T wave in lead one with reciprocal changes in lead three, thus confirming the diagnosis. Following treatment he made an uneventful recovery and has remained well for three years.

CASE NO. 5.—A male, fifty-two years of age, was admitted to the University Hospital complaining of cough, dyspnea, and pain in the right chest of eighteen months' duration. The illness began with pain in the region of the right nipple which was associated with cough and shortness of breath. The pain and cough increased in severity until relief could only be obtained by sitting up in bed bending forward. Physical examination of the heart showed no enlargement. No murmurs were heard, the sounds being clear and distinct. The blood pressure was systolic 100 mm., diastolic 80 mm. A visible and palpable impulse was found at the second interspace to the right of the sternum with increased retro sternal dullness. A diagnosis of aneurysm of the aorta was made and confirmed by roentgenograms of the chest. At autopsy a ruptured aneurysm of the aorta was found (fig. 1).

Certain criteria should always be sought in studying murmurs:

- (1) The presence, or absence, and the quality of the heart sounds,
- (2) the location of the murmur, i.e. the area at which it is best heard, e.g. mitral, aortic, tricuspid or pulmonary,
- (3) the time of the murmur in the cardiac cycle,
- (4) the duration of the murmur,
- (5) the quality, the pitch, and the intensity of the murmur,
- (6) the transmission of the murmur,
- (7) the effect on the murmur of posture, respiration and exercise.

These criteria should be carefully and routinely determined. Each has its importance. First of all, it is essential to ignore the

murmur and determine the characteristics of the heart sounds that are present. Then the murmur itself is studied. The area where the murmur is best heard should be determined. Every effort should be made accurately to time the murmur, it may be heard early, late or throughout the cardiac cycle. Accurate timing is sometimes difficult especially when tachycardia is present, murmurs classified as pre-systolic are often found to be mid-diastolic in time when the heart is slowed. The duration of the murmur may have significance, e.g. long murmurs replacing the sounds usually indicate an organic lesion, although short murmurs may be equally significant. The quality of the murmur may be rasping, rough or blowing, and should not be confused with the intensity. The pitch of a murmur has greater significance than the intensity. The presence or absence of transmission of the murmur should be noted, as well as the effect on the murmur of posture, respiration and exercise. Special procedures such as the inhalation of amyl nitrite may give valuable information. It must be remembered that the integrity of the heart muscle, and the rhythm and rate of the heart beat greatly affect the accurate timing, duration, intensity and transmission of the murmur.

The gravity of the lesion should not be judged by the quality and intensity of the murmur. Failure to appreciate this has led to serious errors. In decompensated hearts it is not unusual for faint murmurs to become louder as the myocardium improves, and then be detected by less skilled and less thorough ears for the first time. In acute bacterial endocarditis murmurs may be absent, or so faint and variable that their detection is difficult. This variability in intensity from day to day in itself may aid in the diagnosis of the endocarditis. Another example of a grave condition in which the murmurs are sometimes faint is acute rheumatic endocarditis in childhood affecting either the mitral or aortic valves. To ignore these murmurs because they are faint and, therefore, to assume that they are of little significance is a serious mistake and may prove harmful to the patient. Experience has shown that these early manifestations are often incorrectly interpreted and hence valuable time is lost in establishing the proper treatment. As can be seen, in none of these instances was the intensity of the murmur an index of the severity of the underlying lesion. Physicians show ignorance of these facts when they

remark that faint murmurs requiring careful examination for their detection are without significance

CASE No 6—A male, twenty seven years of age, was admitted to the University Hospital, January 18, 1932, complaining of weakness, cough and chills with fever. The illness began six weeks before with sudden chest pain, chill and cough associated with an elevated temperature and rusty sputum. His physician found signs of pneumonia. He gradually improved until the eighth day when recurrent chills and wide temperature fluctuations occurred. During the following three weeks the chest was repeatedly aspirated for suspected empyema with negative results. He was then removed to the University Hospital and came under my care. Examination showed pallor, dyspnea, prostration, dullness, bronchial breathing and moist rales in the right mid lung field and moist rales at the left base. A very faint systolic murmur was heard along the left border of the sternum. It varied in intensity from day to day so that on some days it was not heard, whereas on other days it was faint but detectable. My assistants disagreed as to the existence of a murmur. Palpable spleen and leukocytosis were present. Repeated blood cultures revealed Type 1 pneumococcus. Autopsy showed acute bacterial endocarditis with friable vegetations on the tricuspid valve and on the wall of the right auricle. The other valves were free from vegetations. Numerous infarctions of both lungs were found with lobar pneumonia (fig 2).

It is customary to divide heart murmurs into two main groups, (1) Organic, (2) Functional. While every effort should be made thus to classify them, it is obviously more important to determine the cause of the murmur, for the condition producing the functional murmur may be more serious than that causing the organic murmur. Murmurs are spoken of as systolic, presystolic, or diastolic in relation to the time of occurrence in the cardiac cycle, and as mitral, aortic, pulmonary, or tricuspid in relation to the area over which they are best heard.

SYSTOLIC MURMURS

Mitral—A systolic murmur heard at the apex when the patient is in the prone position and which disappears when the patient is in the upright position is commonly heard and is without significance. In fact this type of murmur, influenced by posture, is frequently heard over the entire precordium. The mitral systolic murmur without cardiac enlargement is commonly heard in febrile states and should not be considered evidence of organic disease as it is usually without significance. However, if there is a history of rheumatic infection it may be necessary to reserve opinion until further observa-

tions and studies have been made. The appearance of other murmurs would strengthen the diagnosis of an organic lesion. Often it is impossible from one examination to determine whether or not an organic lesion is present. Time and repeated examinations with careful correlation of all symptoms may be necessary before the correct diagnosis can be made.

It is of prime importance to consider the age of the patient. In childhood and early adult life mitral systolic murmurs should immediately suggest rheumatic fever. A history of tonsillitis, growing pains, epistaxis, chorea, unexplained rash, fever, or other ill defined illnesses in childhood, may strengthen the diagnosis of rheumatic valvulitis. It is important to realize that the history may be entirely negative, and the systolic murmur be the first sign of rheumatic fever. An increased sedimentation rate of the blood and electrocardiographic evidence of conduction disturbance may aid in the diagnosis of an organic lesion. If the murmur partially or completely replaces the first sound, is loud and is transmitted into the axilla and the back, regurgitation associated with valvulitis and dilatation of the ring is likely. Enlargement of the heart would be further evidence of an organic lesion.

In young and middle aged patients mitral systolic murmurs with definite cardiac enlargement indicate organic lesions. Careful search for the cause of the enlargement may disclose aortic valvulitis, hypertension or chronic adhesive pericarditis.

An apical systolic murmur in a middle aged individual in the absence of cardiac enlargement but with a definitely palpable thrill, an abnormally forcible first sound, a mitral mid-diastolic murmur, and an accentuated pulmonary second sound may be due to stenosis of the mitral valve. Occasionally the systolic murmur of regurgitation may be the only murmur heard, and the more important mid-diastolic rumble of stenosis missed unless the patient is very carefully examined for such evidence. The stenotic murmur sometimes is heard best following exercise or inhalation of amyl nitrite or with the patient lying on the left side.

The systolic mitral murmur heard in elderly patients is usually due to insufficiency of the mitral valve, secondary to hypertrophy and dilatation of the left ventricle from coronary sclerosis and chronic myocarditis. The history may reveal symptoms of myocardial fail-

ure, following a previous attack of coronary occlusion, progressive myocardial fibrosis, or long continued hypertension. However, the murmur may be transmitted from pathological changes at the aortic ring.

A systolic murmur heard over the other areas as well as at the mitral would indicate a loss of muscular tone suggesting anemia or increased velocity of the blood flow. Hyperthyroidism may explain the presence of a systolic murmur at the apex especially if accompanied by forcible heart sounds, tachycardia, high pulse pressure, increased systolic tension and elevated basal metabolic rate. A rare cause of mitral systolic murmurs is a congenital lesion. A systolic murmur is sometimes heard at the mitral area, which is found to disappear with cessation of respiration. It is functional and without significance, and is termed a cardio-respiratory murmur.

Aortic—An aortic systolic murmur may be caused by a number of conditions aortitis, aortic aneurysm, aortic atheroma with roughening of the cusps, aortic stenosis, and finally, it may occur in the absence of organic disease. The murmur may have a soft or harsh quality. The soft murmurs are usually not transmitted, whereas the loud harsh murmurs are well transmitted.

Again the age of the patient is of importance in determining the significance of an aortic systolic murmur. In infancy aortic systolic bruits suggest rheumatic fever, in middle age, aortitis due to syphilis or previous rheumatic infection, in advanced years, arteriosclerotic changes of the aorta, or the ring or the cusps of the aortic valve.

The quality, the intensity, and the transmission of the aortic systolic murmur is important. The murmur may be transmitted into the neck or down along the left border of the sternum or particularly well to the apex. It is necessary to remember that a systolic murmur of aortic origin is sometimes best heard at the apex.

The possibility of aortic stenosis should always be considered. Years ago it was thought to be a rare lesion, but today it is diagnosed more frequently because an increasing number of physicians are suspecting this lesion to be present until proved otherwise and are diagnosing more accurately. Every attempt should be made either to eliminate or to establish the diagnosis of aortic stenosis because of the extreme importance of this diagnosis to the future welfare of the patient. Before the diagnosis of aortic stenosis is definitely made

other confirmatory signs should be elicited, namely, a palpable thrill over the aortic area and the special characteristics of the aortic second sound. The latter, when carefully studied, is usually found diminished in intensity or entirely absent. The finding of cardiac hypertrophy strengthens the diagnosis. In the early stages of aortic stenosis the palpable thrill in the aortic area, the cardiac hypertrophy and the changes in the second sound may not be present, and the systolic murmur may be the only sign present. It then becomes important to differentiate it from aortitis—in order that the patient may receive proper treatment if aortitis is present and not be given unnecessary treatment if aortic stenosis exists. In these instances careful fluoroscopic examination is an invaluable diagnostic aid because definite calcification of the aortic cusps indicating stenosis or dilatation of the first part of the aorta suggesting aortitis may be visualized thus establishing the diagnosis. Sosman and Wosika¹ first directed attention to the importance of the fluoroscopic examination in the diagnosis of aortic stenosis. An aortic systolic murmur is sometimes heard with aneurysm affecting the first portion of the aorta. Aortic systolic murmurs without diagnostic importance are frequently heard in over-acting hearts and not infrequently heard in severe anemia.

Pulmonary and Tricuspid—The pulmonary area has been repeatedly referred to as the area of cardiac romance. Systolic murmurs are very frequently heard at this area and may or may not be of significance. They are commonly found in individuals with normal hearts. In this group the murmur is usually heard when the patient is in the prone position. An abnormal relationship between the chest wall and the pulmonary artery is considered to be the cause of the murmur. Unfortunately because of this murmur, pulmonary stenosis may be erroneously diagnosed and the patient told that he has organic valvular heart disease. Pulmonary stenosis is a rare lesion, usually of congenital origin. It should be diagnosed only when other signs, such as a palpable thrill in the second left interspace, and diminution or absence of the pulmonary second sound are also present.

The systolic murmur at the tricuspid area is due to regurgitation and is usually functional, and secondary to hypertrophy and dilatation of the right ventricle associated with mitral disease. If it is due

to organic disease it rarely occurs without evidence of involvement of the other valves

DIASTOLIC MURMURS

Mitral—A mitral diastolic murmur may be due to changes at the valve, either relative or organic, or it may be referred from aortic valve disease. In the discussion of the diastolic murmur due to stenosis it is unfortunate that the terms presystolic and mid-diastolic are used. These terms relate to the time of the murmur in diastole, and are an indication of the degree of stenosis, however, it is not generally known that they are descriptions of the same murmur. In some instances the increased speed of the heart gives prominence to the presystolic phase of the murmur. In other instances, when the heart is sufficiently slow or when auricular fibrillation is present, the murmur is best heard in mid diastole. The mid-diastolic murmur is the more important to hear. When the heart rate is rapid, the presystolic bruit may be so close to the first sound as to appear a part of this sound, and it may then be confused with the abnormal first sound of an over-acting heart. Failure to recognize the presystolic or mid-diastolic murmur is often due to lack of familiarity with some of its essential characteristics *viz*,

- (1) The peculiar rumbling, roll of a drum quality
- (2) The localization to a small area sometimes not larger than that covered by the bell of the stethoscope
- (3) The maximum audibility when the patient is examined lying on his left side

Presystolic mitral murmurs are usually considered evidence of mitral stenosis, and all the more so when there are present the other signs of mitral stenosis, namely (1) palpable thrill, (2) forcible first sound, (3) increased dullness in the second and third left interspaces, and (4) accentuated pulmonary second sound. Again the history of rheumatic fever is a valuable aid. An electrocardiogram showing right axis deviation and a roentgenogram showing a prominent left auricle would strengthen the diagnosis. However, presystolic murmurs do not always indicate organic mitral stenosis. There are several exceptions, and lack of familiarity with them has been responsible for errors in the diagnosis of mitral stenosis. One of the more

common mistakes is to interpret the abnormal first sound in over-acting hearts as a presystolic murmur. This was frequently done during the World War. Other conditions in which presystolic and diastolic murmurs have been heard with no evidence of mitral stenosis found at postmortem are aortic regurgitation with an Austin Flint murmur,² chronic adhesive pericarditis,³ acute rheumatic myocarditis in children,⁴ chronic pulmonary disease with cardiac hypertrophy,⁵ hypertensive heart disease with massive left ventricular hypertrophy,⁶ congenital lesions,⁷ and tumors of the left auricle.⁸

A mitral diastolic murmur other than the Austin Flint murmur may be found with aortic regurgitation. It has a soft blowing quality and may form a part of, or entirely replace the second sound. Attention to these characteristics will enable the observer to differentiate it from the presystolic Flint murmur or from the other murmurs indicating or simulating mitral stenosis.

Aortic.—The aortic diastolic murmur is due to regurgitation through the aortic valve from either relative or organic lesions. Relative aortic regurgitation may result from dilatation of the aorta, with aortitis or hypertension, from massive cardiac dilatation, or from severe anemia. Aortic regurgitation may be due to (1) congenital defect, (2) acute bacterial endocarditis, (3) rheumatic valvulitis, (4) syphilitic valvulitis, (5) sudden rupture of the cusp from trauma or infection. The murmur has a soft blowing quality, and its duration and effect upon the second aortic sound may indicate the extent of the lesion. A murmur of short duration with a well preserved second sound would indicate a slight lesion, whereas a murmur of longer duration partially or completely replacing the second sound would indicate more extensive damage. The bruit may be elicited over the aortic area, along the left border of the sternum, at the ensiform cartilage, or at the apex, but is usually best heard at the third left interspace. When the aortic lesion causing the regurgitation is not complicated by stenosis, various vascular phenomena resulting from high pulse pressure are present. These include capillary pulsation, Corrigan pulse, pistol shot sounds, and Durozicz's sign. When it becomes necessary to differentiate an aortic diastolic from a pulmonary diastolic murmur the presence of these vascular phenomena is of considerable assistance and favors the diagnosis of aortic regurgitation, whereas evidence of mitral stenosis with an electro-

cardiogram having definite right axis deviation and a roentgenogram showing an enlarged left auricle would suggest the diagnosis of pulmonary regurgitation. In the latter instance, the pulmonary diastolic murmur is due to relative pulmonary regurgitation, first described by Graham Steel. Organic pulmonary regurgitation is a rare condition usually associated with pulmonary stenosis. Tricuspid stenosis is uncommon and rarely diagnosed ante mortem.

CONTINUOUS MURMURS

Certain continuous murmurs having a humming quality are found in congenital lesions. These murmurs occupy both cycles of the heart, and need not cause confusion, if careful examination is made. The two most frequent congenital lesions having such murmurs are (1) patent ductus arteriosus and (2) patent interventricular septum. The murmur in patent ductus arteriosus is found in the second space to the left of the pulmonary area, whereas that due to patent interventricular septum is best heard in the middle and to the left of the sternum.

FRiction RUBS

Adventitious sounds, called friction rubs, which are not exactly related to the cardiac cycle are found in pericarditis. These sounds are more superficial, seemingly closer to the ear than endocardial sounds, are increased by pressure of the stethoscope, and are influenced by changing the patient's position. They may be heard only at the base and are apt to be confused with endocardial murmurs. Careful attention to the characteristics of the sounds, and lack of other evidence of endocardial disease will enable one to differentiate them.

ARTERIAL AND VENOUS MURMURS

Murmurs having a distinctive humming quality are frequently heard over the large blood vessels in normal individuals. These murmurs deserve mention because they are sometimes assumed to be of cardiac origin. There is usually no difficulty in identifying them, since they are found in places outside the cardiac area. Organic, arterial and venous lesions producing such murmurs are rare, when they do occur they are usually either congenital or due to trauma or infection, e.g. arteriovenous aneurysm.

CONCLUSIONS

Heart murmurs may be present without organic cardiac disease. Serious heart disease may be present without detectable murmurs. Faint murmurs must not be considered to be without significance. The intensity of the murmur is not an index of the gravity of the underlying condition. The cause of a murmur is far more important than whether it is classified as organic or functional. Auscultation should not be used alone to make a diagnosis, especially not to make a diagnosis of cardiac disease. The history, physical examination and laboratory evidence must be considered in evaluating every murmur. Do not tell the patient he has no cardiac disease because no murmur is found, likewise do not tell every patient who has a murmur that he has cardiac disease. The efficiency of the heart muscle is often more important than the murmur in the diagnosis of cardiac disease.

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CLINIC ON PERIPHERAL VASCULAR DISEASES*

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THE rapid progress which has been made during the past few years with reference to the diagnosis and management of the peripheral vascular disturbances has resulted mainly from the phenomenal growth of accurate clinical and experimental observations rather than from any one new or dramatic discovery. It is certainly true, however, that during these years many new discoveries have been made, but most of them have proved of little immediate value to the physician who must treat these disturbances in his everyday practice. All of these discoveries when taken together, however, comprise an impressive contribution to our knowledge of the way in which arterial disturbances manifest themselves and how the serious consequences of arterial insufficiency in human extremities can be prevented.

This renewed interest in the practical aspect of these disorders has likewise yielded information which gives all of us a much clearer conception of the mode of onset of changes in the peripheral distribution of arterial blood and the way in which such disturbances produce their symptoms. Simple tests for vascular function and capacity in man have been devised in order that early changes in arterial blood flow in the extremities can be recognized and their seriousness properly evaluated before some irreparable damage, to the tissue of the distal part of that extremity, has taken place. Thus a better understanding of the pathologic-physiology of the circulation under such condition has eventually led to the development of simpler methods of treatment with reemphasis upon the older methods of general care which have always played an important part in preventing some of the more serious complications of arterial insufficiency in the extremities.

In spite of all of this work a large proportion of patients with peripheral vascular disturbances are seen by their physicians or their ailment properly diagnosed only after some serious complication such as infection or gangrene has actually made its appearance. We must

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all make a determined effort to recognize these disorders in their early stages and to institute proper treatment before the process extends to the stage where amputation of the affected part is all that remains to be done. In order to do this we must have a clear idea of the type of pathologic or pathologico-physiologic processes in the arteries which might give rise to the signs and symptoms which are undisputable evidence of arterial insufficiency to the tissues of an extremity.

There are many ways of segregating, into groups, the various peripheral vascular disturbances but we have found that a classification based upon the nature of the particular disturbance is, in the long run, the most useful for ordinary clinical purposes. We prefer, therefore, to use the following classification:

I Peripheral Vascular Disturbances

A Vasomotor or functional disturbances

a Vasoconstrictor disturbances

1 Raynaud's Syndrome

2 Acrocyanosis (Acroasphyxia chronica, Acroparaesthesia, Sclerodactyly)

b Vasodilatory Disturbances

1 Erythromelalgia

2 Acute Painful Osteoporosis (?)

B Organic Diseases of the Arteries

a Traumatic (Chemical and Thermal)

1 Embolism and Simple Thrombosis

2 Arteriovenous Aneurysm

3 Phenol and all caustics

4 Frost bite

b Inflammatory (Toxic)

1 Thromboangiitis obliterans

2 Specific Arteritis (Syphilis Periarteritis nodosa)

3 Non specific Arteritis (Exanthemata, Typhus, Typhoid, Pneumonia)

4 Non specific Arteritis (Chronic toxemia, Ergotism)

5 Endarteritis obliterans (Cause undetermined)

c Degenerative changes

1 Arteriosclerosis (Senile, Diabetic)

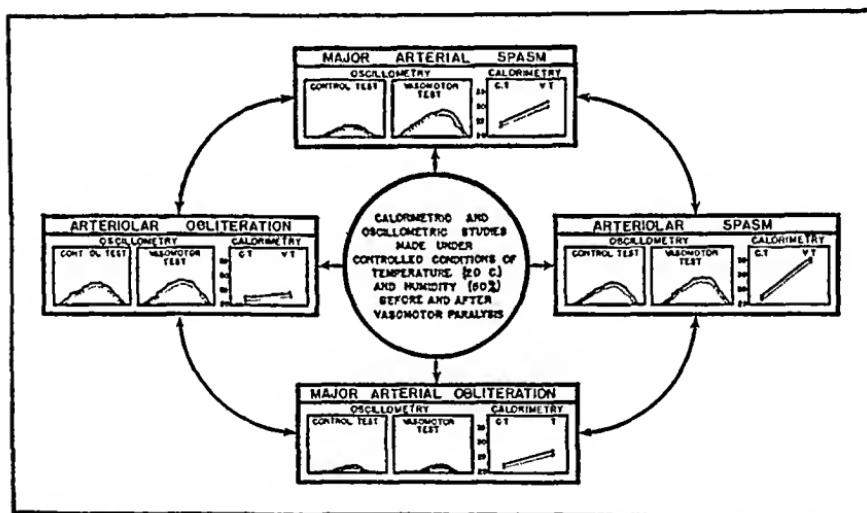
2 Mönckeberg's Medial Sclerosis

Clinical experience has shown that there are many major factors which influence the circulation of arterial blood in the distal parts of an extremity, yet, in final analysis, the basic disturbance in the physiology of the peripheral arterial circulation is relatively the same for many of these factors. These factors which are responsible for alteration of the peripheral distribution of arterial blood can easily be summarized in the following manner:

- A. Physical state of the intravascular fluid,
 - 1 Quantity
 - 2 Pressure
 - 3 Viscosity
- B Physical state of the peripheral arteries,
 - 1 Abnormal spasm
 - 2 Rigidity
 - 3 Compression
 - 4 Obliteration
- C Physical factors in the environment,
 - 1 Atmospheric pressure
 - 2 Temperature
 - 3 Radiation (light)

In clinical practice, therefore, we have come to consider that all deficiencies of the peripheral arterial circulation result from a com-

FIG. 1



Changes in the oscillometric and calorimetric readings which characterize the four main types of arterial disturbances responsible for deficiencies of the peripheral distribution of arterial blood. Any combination of these types may be seen in clinical practice.

bination of two or more of the four major disturbances which alter the physiology of the peripheral arteries, namely, major arterial spasm, major arterial obliteration, arteriolar spasm or arteriolar obliteration. An accurate differentiation between these types can be made under controlled conditions of temperature and humidity by oscillometric and calorimetric studies made before and after complete vasoconstriction (fig. 1).

For the proper clinical evaluation of the problem by the practitioner, however, such elaborate tests are not absolutely necessary since it is possible to obtain all of the essential data by careful physical examination with ordinary equipment. Emphasis will be placed upon the simpler means of determining the relative proportion of both spasm and obliteration which are responsible for the vascular insufficiency during the discussion of each of the clinical cases presented in this clinic. In order to bring out more clearly the important points in the diagnosis and treatment of some of the common forms of peripheral vascular disturbances we should like to present a few typical cases for your consideration.

RAYNAUD'S SYNDROME

DR. ALOIS MOORE This patient, a white girl, age fourteen years, was first admitted to the Children's Hospital on March 5, 1934, with the following history and complaints. For several years prior to her first admission to the hospital the patient noticed that her arms and legs became mottled in appearance when she became fatigued. The feet and hands appeared pale and were subjectively cold and numb. During the winter months of 1933-1934 these color changes appeared more frequently and were more pronounced until the arms and legs became slate-blue in color during each attack. The legs and arms were always involved simultaneously. Excitement, fatigue and cold seemed to bring on these color changes in the extremities. Complete laboratory and clinical studies at that time failed to reveal any cause for these vascular manifestations. She was discharged to her home for further observation. On July 26, 1935, she was again admitted to the hospital because her symptoms had steadily grown worse and she had developed impetigo on both lower legs. At this time complete vascular studies were done and the circulatory insufficiency was shown to be due to high grade spasm of the peripheral arterics without any evidence of organic changes in these arteries. The blood pressure was systolic 115, diastolic 65 at the time of this examination and the urinalysis, blood smear, total and differential blood cell counts, and blood chemistry were normal and the Wassermann reaction was negative. The basal metabolic rate was increased 15 per cent.

DR. LOUIS G. HEREMANN We are dealing here with a girl who is just entering adolescence and presents a problem which is of great

concern to herself, her parents and her physician. It is not unusual to see mild vasomotor disturbances in girls at or near puberty especially if that girl is of the tall, thin, awkward type which we frequently refer to as the hyperpituitary type. The vasomotor changes in this latter group of young girls are transient and rarely cause more clinical signs than cold, clammy hands with a faint reddish-blue cast to the skin when the extremities are not well protected from cold. Usually, careful attention to keeping the hands warm at all times will prevent any further complications and within a year or so the signs of vasomotor instability gradually disappear. When these signs and symptoms persist we have found that the administration of theelin (2000 units in oil) intramuscularly at intervals of seven days for twenty-four injections, will usually cause the vasomotor disturbances to disappear and the patient to become free from her former symptoms. This type of therapy was carried out for this patient but only temporary relief from the symptoms resulted. The impetigo contagiosa was treated successfully by the use of local applications of a 5 per cent aqueous solution of Gentian Violet. I would like to have Dr. Moore tell us how he arrived at the diagnosis of high grade peripheral arteriospasm without organic disease of the arteries.

DR. MOORE After the patient had had all her extremities exposed, for one hour, in a constant temperature room where the environmental temperature was 20° C (68° F) and the relative humidity was approximately 50 per cent, accurate determinations of the surface temperature of the toes and fingers were made and oscillometric curves plotted to determine the elasticity of the major arteries in all the extremities. The surface temperature of the fingers and toes in these control studies showed an average temperature of 23° C which signifies a marked deficiency in the arteriolar circulation in the distal parts of all of the extremities. The oscillometric curves showed moderate restriction of the elasticity of the major arteries of all four extremities. The patient was then wrapped in blankets, according to the method of Coller and Maddock, to cause vasomotor relaxation. After one hour the temperature of the fingers and toes had risen 11° C and the oscillometric curves showed normal elasticity of the major arteries. This is undeniable evidence of marked instability of the vasomotor system and proof that the arterial insufficiency in this patient was the result of high grade arterial

For the proper clinical evaluation of the problem by the practitioner, however, such elaborate tests are not absolutely necessary since it is possible to obtain all of the essential data by careful physical examination with ordinary equipment. Emphasis will be placed upon the simpler means of determining the relative proportion of both spasm and obliteration which are responsible for the vascular insufficiency during the discussion of each of the clinical cases presented in this clinic. In order to bring out more clearly the important points in the diagnosis and treatment of some of the common forms of peripheral vascular disturbances we should like to present a few typical cases for your consideration.

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DR. ALOIS MOORE This patient, a white girl, age fourteen years, was first admitted to the Children's Hospital on March 5, 1934, with the following history and complaints. For several years prior to her first admission to the hospital the patient noticed that her arms and legs became mottled in appearance when she became fatigued. The feet and hands appeared pale and were subjectively cold and numb. During the winter months of 1933-1934 these color changes appeared more frequently and were more pronounced until the arms and legs became slate-blue in color during each attack. The legs and arms were always involved simultaneously. Excitement, fatigue and cold seemed to bring on these color changes in the extremities. Complete laboratory and clinical studies at that time failed to reveal any cause for these vascular manifestations. She was discharged to her home for further observation. On July 26, 1935, she was again admitted to the hospital because her symptoms had steadily grown worse and she had developed impetigo on both lower legs. At this time complete vascular studies were done and the circulatory insufficiency was shown to be due to high grade spasm of the peripheral arteries without any evidence of organic changes in these arteries. The blood pressure was systolic 115, diastolic 65 at the time of this examination and the urinalysis, blood smear, total and differential blood cell counts, and blood chemistry were normal and the Wassermann reaction was negative. The basal metabolic rate was increased 15 per cent.

DR. LOUIS G. HERREMAN. We are dealing here with a girl who is just entering adolescence and presents a problem which is of great

concern to herself, her parents and her physician. It is not unusual to see mild vasomotor disturbances in girls at or near puberty especially if that girl is of the tall, thin, awkward type which we frequently refer to as the hyperpituitary type. The vasomotor changes in this latter group of young girls are transient and rarely cause more clinical signs than cold, clammy hands with a faint reddish-blue cast to the skin when the extremities are not well protected from cold. Usually, careful attention to keeping the hands warm at all times will prevent any further complications and within a year or so the signs of vasomotor instability gradually disappear. When these signs and symptoms persist we have found that the administration of theelin (2000 units in oil) intramuscularly at intervals of seven days for twenty-four injections, will usually cause the vasomotor disturbances to disappear and the patient to become free from her former symptoms. This type of therapy was carried out for this patient but only temporary relief from the symptoms resulted. The impetigo contagiosa was treated successfully by the use of local applications of a 5 per cent aqueous solution of Gentian Violet. I would like to have Dr. Moore tell us how he arrived at the diagnosis of high grade peripheral arteriospasm without organic disease of the arteries.

DR. MOORE: After the patient had had all her extremities exposed, for one hour, in a constant temperature room where the environmental temperature was 20° C (68° F) and the relative humidity was approximately 50 per cent, accurate determinations of the surface temperature of the toes and fingers were made and oscillometric curves plotted to determine the elasticity of the major arteries in all the extremities. The surface temperature of the fingers and toes in these control studies showed an average temperature of 23° C which signifies a marked deficiency in the arteriolar circulation in the distal parts of all of the extremities. The oscillometric curves showed moderate restriction of the elasticity of the major arteries of all four extremities. The patient was then wrapped in blankets, according to the method of Coller and Maddock, to cause vasomotor relaxation. After one hour the temperature of the fingers and toes had risen 11° C and the oscillometric curves showed normal elasticity of the major arteries. This is undeniable evidence of marked instability of the vasomotor system and proof that the arterial insufficiency in this patient was the result of high grade arterial

spasm and not the result of some organic disease of the peripheral arteries

DR HERRMANN I certainly agree with the deductions which Dr Moore has made from his complete vascular studies of this patient but I fear that such elaborate equipment is out of the question for you who are engaged in the practice of medicine. For controlled scientific study such elaborate tests are actually necessary but there are many other ways of obtaining sufficient data to permit you to arrive at the same conclusion. Dr Rudolph Matas has for many years advocated the use of the ordinary sphygmomanometer to determine the height of the oscillations of major arteries. Many different methods of bringing about vasomotor relaxation have been described and it is largely the question of convenience of use that helps us decide which one is to be employed. We have found that the method described by Gibbon and Landis, which consists of immersing the hands and forearms in water at approximately 42° C is most satisfactory for practical studies. The feet which are to be tested for the vasospasm, are first exposed to the cool atmosphere of an examining room for about fifteen minutes, and the degree of coldness of the skin of the toes noted by measuring the temperature with an ordinary thermometer or by estimating the temperature by feeling the toes with the back of the hand, then the hands are placed in the hot water for an equal length of time. If the diminution of the skin temperature was due to spasm of the arterioles, the reflex vasodilatation will cause the toes to become warm and pink within about ten minutes. If, on the other hand, there is organic disease of the peripheral arteries there will be either no appreciable rise in the temperature of the toes or the moderate rise which does finally take place will be delayed for fifteen or more minutes.

Now that we have arrived at the proper explanation for this patient's complaint let us hear from Dr Moore what the subsequent course of her illness has been and what further therapeutic measures should be considered.

DR MOORE On February 27, 1937, this girl was admitted to the hospital for the fifth time with the story that all of the endocrine therapy had given only temporary relief and that during the past winter her symptoms were very severe, the attacks of discoloration came on more frequently and the skin of her hands and feet was cold and clammy most of the time. She has been having considerable

trouble with infection about the toe nails and on several occasions incision and drainage of paronychia had to be performed. The coldness of the feet has recently made her feet ache so much that she had to stay home from school. We are of the opinion that this patient's present disability is sufficient to justify operative intervention.

DR. HERRMANN Now that sufficient time has elapsed since the onset of this patient's complaint to assure us that there is no chance for spontaneous improvement to take place and since intensive therapy with the various endocrine products has failed to give lasting relief, the consideration of the surgical means of relieving these symptoms should be in order. I can not emphasize too strongly that we are dealing with a young girl and the risks of any major surgical procedure must be carefully weighed before we make such an important decision. With this decision already made by the patient and her parents the question arises, what then are the surgical procedures which offer lasting relief from this atypical variety of Raynaud's syndrome? Certainly experience has demonstrated that either the lumbar sympathetic ganglionectomy or ramisection will bring about permanent paralysis of the vasomotor nerves to the vessels of the lower extremities. These operations can be done either by the retroperitoneal approach from the flanks or both sides can be done at the same time by the transperitoneal approach from a mid-rectus incision on the left side. For permanent vasomotor paralysis to a lower extremity, it is necessary to interrupt all of the pathways connected with the second, third and fourth lumbar sympathetic ganglia. This operation is one of considerable magnitude and should only be done by one experienced in this type of neurosurgery.

DR. MOORE This operation of bilateral lumbar sympathetic ganglionectomy by the transperitoneal route was performed on February 13, 1937, by Dr. Herrmann and we are now presenting the patient to you to demonstrate that her feet are very warm and dry and the color of the extremities remains a normal pink at all times. The pain in the feet has disappeared and the inflammation in the nail bed of the left great toe has subsided. The coldness and slight discoloration of the hands is still present but with the onset of warm weather these symptoms should disappear at least for this season.

DR. HERRMANN We must bear in mind that the high grade vaso-spasm in the upper extremities has been unaffected by the operation.

which has been performed on this patient and when cold weather returns there is no doubt in our minds that the complaints referable to the hands and arms will return. The patient will be restudied this winter and if the findings and complaints are sufficient to justify further surgical intervention the upper extremities will be sympathectomized according to the method of Smithwick and White. I shall describe this operation in detail during my discussion of the next case.

ESSENTIAL HYPERHIDROSIS WITH RAYNAUD'S SYNDROME

DR. JOSIAH SMITH This patient, a white boy, age thirteen years, was brought into the Children's Hospital as a flood refugee on March 10, 1937, because a social worker noticed that the boy would sweat profusely when he became excited. The mother of the child offered the information that this abnormal sweating of the head and arms had been present almost since birth. His mother also added that he had always been a nervous child and not very well developed for his age. The physical examination was entirely normal, except for the profuse sweating of the head, both sides of the face and neck, the upper part of the thorax down to the third costal interspace and both arms and hands. The hands were cold and moist and considerable desquamation of the skin resulted from the constant increased moisture. There was definite mottling of a greyish-blue color over the neck, especially when the beads of perspiration made their appearance on the face, neck and hands. The skin of the face and neck also showed some evidence of desquamation. When the boy was in the resting phase the skin over the affected areas was sometimes very pale and at other times it presented a purplish-red hue, this latter phase was usually followed by the blotchy cyanosis. All laboratory studies were normal. The blood Wassermann reaction was negative. Roentgenograms of the chest and lower cervical region showed a short cervical rib on the right side and a slightly elongated seventh cervical transverse process on the left side. Complete studies of the arterial system of both the upper and lower extremities before and after vasomotor relaxation were made and evidence of marked arterial and arteriolar spasm was found, but no signs of any organic disease of the peripheral arteries or mechanical interference with the flow of blood to either of the upper extremities.

DR. HERRMANN The unusual story certainly points to some cen-

tral (diencephalic) disorder rather than any derangement with the sympathetic nerves in the periphery. The sympathetic nerves control the activities of the sweat glands, consequently, abnormal stimulation of the central (diencephalic) sympathetic centers would give rise to profuse sweating together with other manifestations of overactivity of the sympathetic centers, such as, high grade vasospasm associated with various color changes of the skin from extreme pallor to blotchy cyanosis, over such a well defined area. This boy's problem must be considered unusual since essential hyperhidrosis is usually seen in nervous young women, but even then it is rare to find the disturbance so sharply limited to one part of the body. I am anxious to present this case to you because it carries with it many points of practical value.

The localized or simple forms of hyperhidrosis which are frequently met with in general practice are undoubtedly very mild forms of this same syndrome but usually relief can be obtained by the use of some astringent washes of aluminum sulphate solution or the use of various dusting powders containing alum. The desquamation of the skin between the toes in patients with hyperhidrosis must be carefully differentiated from the type of change in the superficial layers of the skin due to epidermophyton infection. If microscopic examination of the scrapings discloses the presence of this fungus every effort to eradicate the disease should be made since secondary infection of the poorly nourished tissues of the foot may begin from such a break in the epithelium between the toes. We have found that the following fungicide is very efficient in eradicating epidermophyton infection from between the toes of patients with any of the various peripheral vascular disturbances.

EPIDERMOPHYTON COMPOUND

| | |
|-----------------|-----------------|
| Tannic acid | 10 00 Gm |
| Salicylic acid | 5 00 " |
| Menthol | 1 00 " |
| Camphor | 1 00 " |
| Phenol, liquid | 2 00 cc |
| Tincture Iodine | 50 00 " |
| Alcohol, ethyl | q.s ad 100 00 " |

Sig. Apply locally to the lesions at bedtime on three consecutive nights without washing the feet in the meanwhile. Then wash the feet thoroughly with face soap and warm water. Repeat the procedure if any signs of the infection persist.

The simple or localized types of hyperhidrosis have been successfully treated by radiation with roentgen rays but such therapy should only be attempted by an experienced roentgenotherapist and must be done with caution in patients with peripheral vascular diseases.

The fact that the hyperhidrosis in this patient is so marked that his bedclothes become soaked during the night and also that there is associated with the disturbance of sweating such marked vasomotor changes, as Dr. Smith has described to us, makes me feel that conservative therapy will be of little value in this particular case.

DR. SMITH What Dr. Herrmann has said is true for we have been giving this patient theelin intramuscularly without any appreciable improvement. The other vasodilating drugs of the theophyllin group have likewise failed to give any permanent improvement. The extent of the hyperhidrosis makes the local application of astringents extremely difficult and likewise makes the radiation by roentgen rays difficult, as well as, dangerous. With these facts in mind we were of the opinion that surgical intervention was indicated, consequently, on April 19, 1937, Dr. Herrmann performed a complete sympathectomy of the right upper extremity and right side of the face and upper part of the chest and at a second-stage operation done on April 27, 1937, I performed the same operation on the left side. We are presenting the patient here today to show that he has been completely relieved of all of his former symptoms. His face, neck and hands are dry and warm and of the normal pink color. The patient has had no discomfort or untoward effects from the two operations. He has returned to school and now leads the life of a normal boy of his age.

DR. HERRMANN I do not think we should take up the next case without a few more words concerning the operation which was so successful in relieving the patient of a very serious and troublesome disturbance. The old operation of cervicothoracic ganglionectomy or ramisection in which the stellate ganglion (fused inferior cervical sympathetic ganglion with the first thoracic sympathetic ganglion) was removed was not successful in permanently relieving the individuals with Raynaud's syndrome of their symptoms. Most of the patients who were subjected to the resection of the stellate ganglion together with the second and perhaps the third thoracic sympathetic ganglion, returned after a year or eighteen months with many of their former symptoms. The operation of lumbar sympathetic ganglionec-

tomy for the relief of the same syndrome in the lower extremities was never followed by such recurrences, consequently, White, Smithwick, Telford and others set out to determine the explanation for the difference in the results between these two operations. It was brought out by White that the operation of lumbar ganglionectomy interrupted largely preganglionic fibers to the lower extremities, while the old operation of cervical sympathectomy interrupted largely postganglionic fibers to the upper extremities. As a result of much experimental and practical work Smithwick and White found that simple but complete resection of the second and third thoracic sympathetic ganglia with section of the sympathetic chain between the second and third thoracic sympathetic ganglia and finally resection of the proximal one inch of the second intercostal nerve including the junction of the anterior and posterior roots, would interrupt the majority of the preganglionic fibers to the upper extremity and leave the postganglionic fibers intact. This operation is performed from behind and the proximal portion of the second rib together with the transverse process of the vertebra must be removed in order to expose the sympathetic chain and the ganglia. This operation does not produce the objectionable Petit-Horner's syndrome which always followed in the wake of the old type of cervicothoracic sympathectomy.

POSTTRAUMATIC PAINFUL OSTEOPOROSIS

DR. HERRMANN I fear that many of you will feel that the patient whom we are about to present to you should not be included in this discussion of peripheral vascular diseases, nevertheless we shall try to prove to you that the vasomotor and trophic changes which characterize this clinical entity are typical enough to permit us to classify it as one of the functional or vasomotor types of peripheral vascular disease. In addition we are most anxious to bring to your attention this important syndrome in order to impress upon your minds the seriousness of the sequelae which so frequently follow in its wake. I shall ask Dr. Fan to present a summary of the important points in this patient's clinical history together with what he found by physical examination.

DR. H. S. FAN This patient, a white woman, age sixty-two years, was admitted to the hospital on May 14, 1937, because of marked disability of the left hand, constant pain in the hand and wrist associated with marked redness, swelling and increased temperature of the

fingers and hand. She states that about eight weeks before admission to the hospital she slipped and fell on her outstretched hand. She came to the accident ward immediately and roentgenograms of her wrist showed a typical Colles' fracture. The fracture was reduced under local anesthesia without difficulty and without causing the patient much pain. Satisfactory reduction was accomplished and the forearm, wrist and hand were immobilized in a cast of plaster-of-Paris. The patient had no further complaints until about five weeks after the cast had been applied when she began to have pain and swelling of the affected hand. The cast had to be removed because of the increasing amount of pain and swelling of the soft parts of the wrist and hand. At the time the cast was removed, the hand was found to be very hot, the soft tissues were greatly swollen, and the joints of the hand and wrist were stiff. She describes a peculiar aching in the hand which has been constant, dull in character, and of sufficient intensity to keep her from getting the proper amount of rest. In the Fracture Clinic she was advised to take some physiotherapy in the form of baking and light massage, but this only aggravated her pain. She was unable to control the pain by ordinary medicinal measures. She has had no systemic symptoms, her appetite has been good and on physical examination she was found to be in good general health with her pulse rate, temperature and respiratory rate within normal limits. Her blood pressure was slightly elevated. The laboratory studies were all normal and the blood Wassermann reaction was negative. She was referred to the Vascular Disease Clinic where studies of the arterial circulation of the upper extremities showed an increased blood supply to the left hand resulting in an increase in the surface temperature of approximately 3° C even when the patient was placed in the constant temperature room at 20° C. Roentgenograms of the hand showed extensive patchy decalcification of the carpal and metacarpal bones of the left hand, as well as, similar changes in the distal end of the radius and ulna (fig 2). The line of fracture is still visible, but the fragments are in good position and apparently firmly united.

Three days ago a peri-brachial sympathectomy was performed. The swelling of the hand is hardly noticeable now and, as you see, she can flex her fingers almost ninety degrees. The visceral pain has been relieved.

FIG 2



Roentgenogram showing the extensive patchy decalcification of the bones of the left hand and wrist eight weeks after Colles fracture. These changes are characteristic of post traumatic primary osteoporosis. Note the bone fragments are in good position and healing has taken place.

DR HERRMANN We have just heard an interesting account of increasing disability coming on several weeks after the original injury and after the fractured bones had been properly reduced and immobilized in the accepted manner. This story is not an uncommon one and it should immediately bring to your minds the possibility that the new disability might be due to some process which has been superimposed upon the original injury and which has developed as the result of trauma to the periarticular tissues.

It is well known that bones of extremities which have been kept at rest for any considerable length of time lose much of their natural mineral salts, and, consequently, become more permeable to the roentgen rays. This type of bone atrophy is of comparatively little importance since, upon resumption of function of the extremity, the bones rapidly regain their normal density and strength, while during the period of atrophy the patient does not complain of any symptoms which might be referable to the absorption of the mineral salts from the bones.

Not infrequently, however, we find that within three to six weeks after some trivial or serious injury to a polyarticular joint, some patients return to their physicians because of local swelling, redness, constant aching pain and marked stiffness of the previously traumatized joint. The importance of this posttraumatic painful osteoporosis as a cause for the prolonged disability is not widely recognized and many innocent persons with this clinical syndrome are accused of malingering or of being grossly uncooperative. A small number of surgeons have proved their unfamiliarity with this disease entity by recommending too heroic measures, especially amputation of the extremity, for its cure.

At the present there are two main hypotheses concerning the etiology of posttraumatic osteoporosis. The first is that the disease is the direct result of the trauma and that the changes in the bone are brought about by reflex action upon the trophicity or the vascularity of the bone. The second theory is that osteoporosis comes on indirectly and that it is due to inactivity or loss of functional stimulation.

Sudeck showed that the atrophy of inactivity was able to reach a very pronounced degree in amputation stumps, but both Sudeck and Kienbock felt that true osteoporosis comes on much more rapidly than could be explained on the basis of inactivity alone.

True osteoporosis is always characterized by

- (a) loss of motor function of the extremity
- (b) characteristic changes in the roentgenograms
- (c) the constant coexistence of vasomotor and trophic disturbances
- (d) true visceral pain

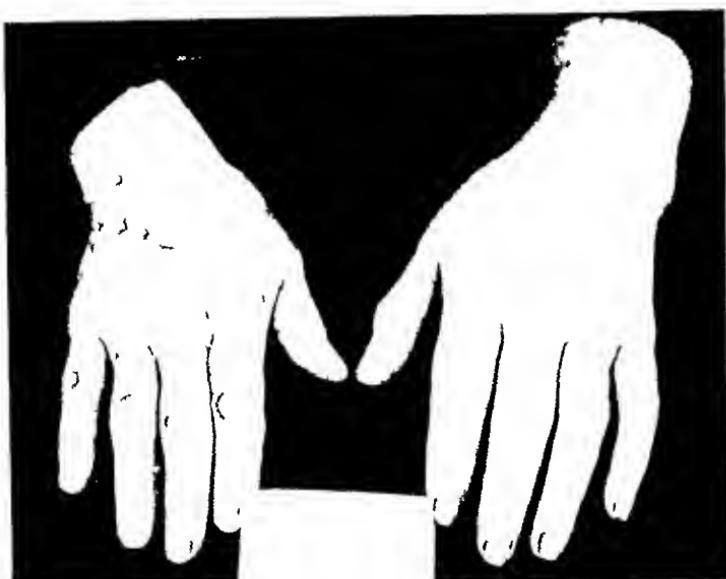
The disturbances of the function are always more extensive than could be explained on the basis of the trauma alone, and the severe acute pain is greatly out of proportion to the local signs of injury to the tissues. If we disregard the local effect of the trauma we must still be impressed by the extensive loss of motor function, the severe constant pain and the obvious vasomotor disturbances. Another almost pathognomonic symptom is that the pain is not relieved by immobilization, while pain associated with simple trauma, fracture of one or more of the bones, or even tuberculous osteo-arthritis is definitely relieved by proper immobilization.

A very common clinical form of true osteoporosis is frequently seen after fractures of the bones of the wrist or ankle which have been properly reduced. After the removal of the bandage or cast at the end of two to four weeks, the extremity is found to be swollen and discolored. Slight active or passive motion of the joint causes the patient great pain. Mechanotherapy, baking and massage make the pain more severe and the loss of function of the extremity continues to become worse. Diathermy gives little or no permanent relief from the pain and in our experience even intensive diathermy does not alter the course of the disturbance. Such a clinical history is typical of true osteoporosis.

From the clinical point of view, the extension of the functional disturbance beyond the area of traumatization and accompanied by constant pain which can not be relieved by immobilization or physiotherapy is indicative of true posttraumatic osteoporosis. In the early stages of the disease the patients complain of "rest pain" of a severe degree, as well as, the inability to bear weight on the affected extremity.

The association of true osteoporosis with cyanosis, subjective and objective sensations of heat, edema and trophic disturbances such as ulcerations, hyperkeratosis, atrophy of the skin and hypertrichosis, and

Fig. 3



Photograph of the hands of the same patient whose roentgenogram is shown in figure 2. Note the swelling of the entire hand and the glossy skin of the dorsum of the hand and fingers. This patient was unable to flex the fingers or wrist.

constant pain have been repeatedly pointed out. Most of the patients show marked muscular atrophy, congestion of the skin of the affected extremity which is accentuated when the limb is placed in the pendant position, marked edema and a thinning of the skin with a disappearance of all of the surface markings giving it a "glossy" appearance (fig 3). When the osteoporosis is limited to the bones of the hands or feet most of the patients have shown a definite hyperthermia of the skin of the distal part of the affected extremity.

Clinical Evolution and Prognosis—It is commonly believed that painful osteoporosis is a self-limited disease and that after a few weeks or months recalcification takes place without leaving any deformities. Sudeck stated that favorable evolution is only occasionally seen and is not the usual end-result of the disturbance. It has been our experience that after the disease has reached the climax or stage of almost complete decalcification, the process of recalcification may begin spontaneously, but years later the roentgenograms still show the thinning of the cortex of the bones and the thin lamellae containing irregular areas of recalcification. From these facts one might get the impression that the disease heals spontaneously since it is also well known that in some instances the vasomotor disturbances and pain may disappear without treatment. In these cases, however, the recovery of function of the extremity requires many years and frequently during the stage of recalcification extensive fusion of the carpal or tarsal bones takes place. This long period of disability followed by ankylosis usually causes great economic loss to the patient. Undoubtedly many of the milder forms of true osteoporosis do heal spontaneously and give no permanent disturbance of function, therefore, one must be careful in assuming that some particular form of therapy used in any one patient is a true remedy for the disturbance.

The treatment of true osteoporosis has, until recently, been symptomatic and preventative rather than curative in nature. Sudeck recommended minimum immobilization and then active movement in most of his cases. In 1926 Nobel and Hauser recommended heat to the point of tolerance either in the form of radiant heat or paraffin baths. They also advised massage and voluntary motion of the joints in spite of a little pain, but they emphasized that forceful manipulation under anesthesia was definitely contraindicated. Any form of fixation with plaster-of-Paris casts or orthopedic apparatus causes

increased pain to the patient, consequently, supports and braces are contraindicated in all cases. Delorme recommended treatment by thyroid and parathyroid extracts and Pech advised heliotherapy. Recently Gurd of Montreal has advised the use of "walking plaster casts" and physiotherapy.

All of these forms of therapy usually leave much to be desired. The course of the disease is only slightly shortened and the unfavorable sequelae are about as frequent as when the process is left untreated.

Our experience in the Cincinnati General Hospital during the past four years during which a total of about sixty patients with true posttraumatic painful osteoporosis came under our observation, has convinced us that the period of disability from this clinical entity can be greatly shortened by properly performing a complete periarterial sympathectomy upon the brachial artery for osteoporosis of the bones of the hand, and upon the superficial femoral artery when the process is limited to the bones of the foot. The technical details for performing the complete removal of the adventitia of any major artery have been described in detail by Lerche, Livingston, White and ourselves. These operations are usually performed under local anesthesia. It is paramount that the operation be done thoroughly and without undue trauma to the delicate branches of the artery, or to the main artery itself.

Operations upon the sympathetic nervous system offer a rational and effective surgical treatment for this disease entity if the operation can be performed during the *acute* phases of the disease process. The relief of pain and the sudden disappearance of the functional impairment has frequently been very striking and the undesirable sequelae of this disease have been prevented. Patients in whom the symptoms were present for more than nine months received very little benefit from these operations.

The patients who were subjected to periarterial sympathectomy were able to resume their work within an average time of three months, while the complete return of function in the control group treated by means of physical therapy together with other conservative measures took more than nine months.

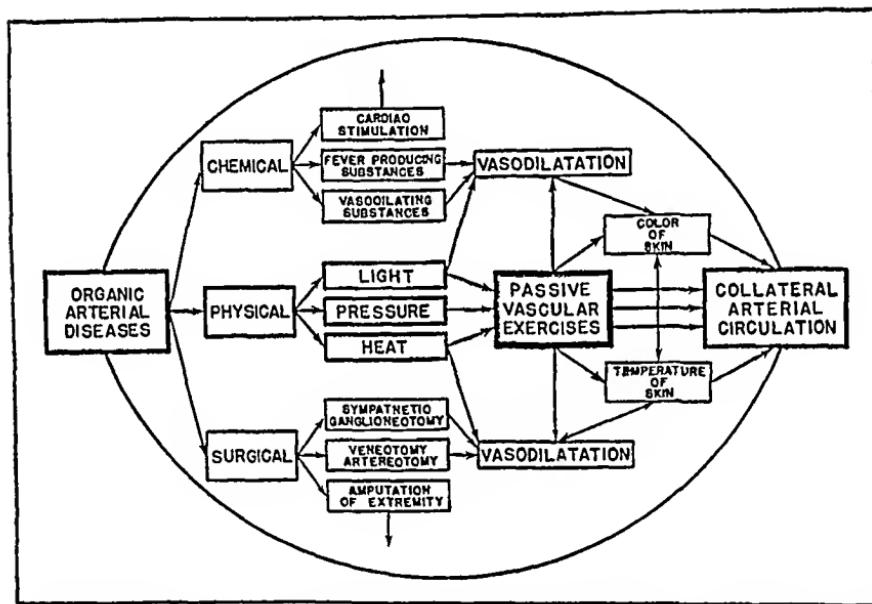
Periarterial sympathectomy is usually sufficient for the early stages in which the process is limited to the distal part of the ex-

tremity Cervical and lumbar sympathetic ganglionectomy or rami-section must be reserved for the extreme forms of the disease

MAJOR ARTERIAL EMBOLISM

The success of any therapeutic method, which is being instituted as an active remedy for the sudden obliterative arterial diseases of the extremities, depends, to a very large measure, upon the efficiency of the collateral arterial circulation which develops as a consequence of the therapy All medicinal methods have for their basis the production

FIG. 4



Various methods of overcoming the deficiency of arterial circulation in patients with organic arterial diseases of the extremities All active therapy should be directed primarily toward the establishment of an adequate collateral arterial circulation

of an active vasodilatation, which experience has shown only favors the development of a collateral arterial circulation about the diseased or injured arteries (fig 4) Frequently some more efficient means of stimulation of the circulation must be resorted to or disaster ensues In order to emphasize to you the means of stimulating the flow of blood through the collateral arterial pathways when the major or secondary pathways are obliterated by a clot or by trauma we should like to present this next patient who more than three years ago was brought to the Christian R Holmes Hospital because of an embolic

occlusion of the right common iliac artery Dr Jean Stevenson will give us the details from her original hospital record

DR JEAN M STEVENSON A white woman, thirty-seven years of age, was brought to the hospital on February 21, 1934 because of exerueriating pain in the entire right leg, the complete loss of muscular function of the leg, anesthesia of the lower third of the leg and foot, together with a eadaverie appearance of the entire right lower extremity The patient had had rheumatic fever at the age of fifteen and subsequently developed mitral stenosis She had never had any signs of cardiae decompensation and apparently went through three normal pregnancies without developing any complications Several days before admission to the hospital, she developed an upper respiratory infection of moderate severity The day following the onset of this infection she noticed that her heart action was irregular in force and rhythm She consulted her family physician who examined her heart and told her that she had auricular fibrillation and advised complete rest in bed without speacial medication Three days later, on awaking in the morning, she noticed that her heart action was more irregular than it had been so she decided to get up and help her children get off to school A short time after getting out of bed, she experienced a severe and sharp pain in the right lower quadrant of the abdomen The pain radiated down the right leg and within a very short time the entire foot became numb On removing her stocking she found that the leg and foot were cold and "dead" white She immediately called her physician and he advised her to go to bed and apply heat to the entire extremity In spite of the oral administration of opiates, the pain continued to grow worse and at the end of several hours she was advised to go to the hospital for relief She reached the hospital approximately five hours after the onset of the pain Examination showed that her entire right leg was ischemic, the foot was cold, sensation was lost and function of the extremity greatly impaired, and no pulses were palpable in any of the peripheral arteries from Poupart's ligament down to the toes The patient's general condition was critical and she was in great agony Her blood pressure was low and her heart rate was rapid and irregular

DR. HERRMANN There is no doubt in our minds that this attack of auricular fibrillation was the direct result of damage from the old rheumatic carditis which originally produced the mitral stenosis in

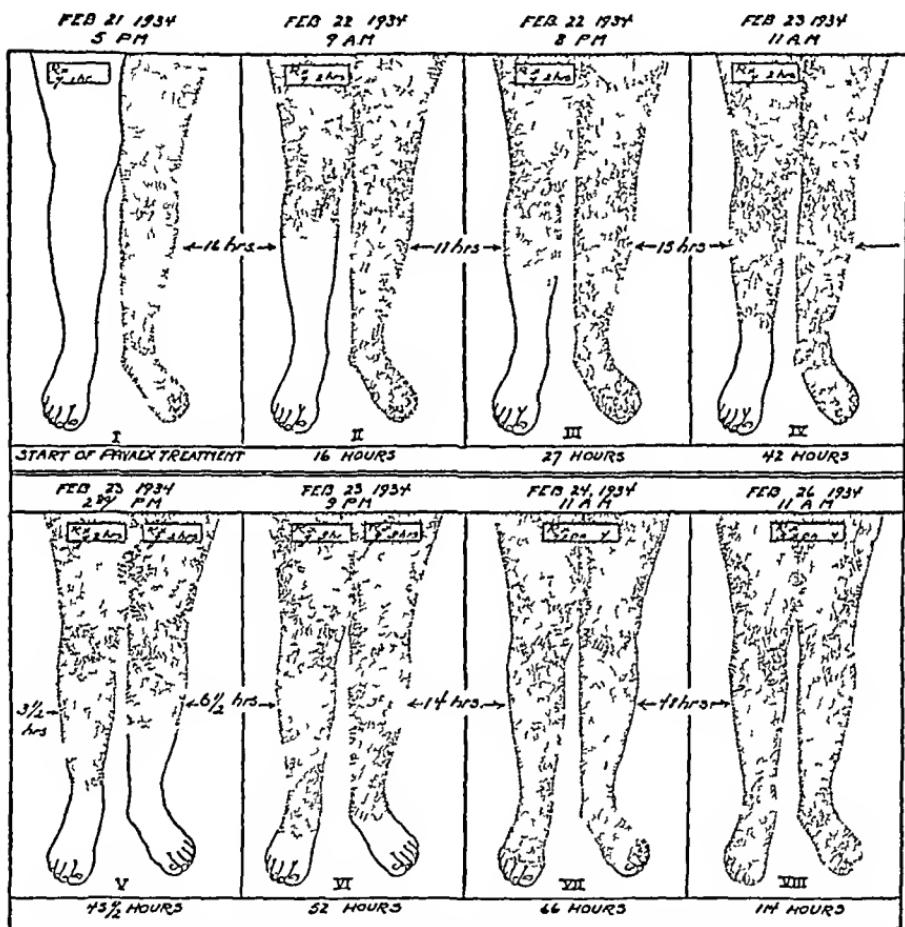
this patient. A blood clot apparently formed within the fibrillating auricle and when the cardiac mechanism suddenly returned to normal the contraction of the auricle caused the clot to be forced out into the left ventricle and thence into the greater circulation and it finally came to lodge at the bifurcation of the right common iliac artery. The sudden abstraction of the necessary amount of blood to the tissues of the distal part of the extremity by the blockage of the main artery, as well as the reflex vasoconstriction of the collateral arterial pathways, together were responsible for the clinical appearance of the extremity. The extreme degree of shock precluded the possibility of operative interference in the form of arteriotomy, for removal of the clot, or any surgical method for the production of vasodilatation, such as lumbar ganglionectomy or ramisection. Dr. Mont Reid suggested that the vasodilatation, which follows the exposure of such an extremity to the rhythmic alternation of the environmental pressure, in the form of passive vascular exercises (fig. 7), might be of value. This was started as quickly as possible and we shall hear from Dr. Stevenson about the subsequent hospital course of this patient.

DR. STEVENSON. After about twelve minutes of passive vascular exercises, a definite pink color appeared over the right patella. Very rapidly thereafter, the pink color descended toward the toes and as this wave of arterial blood rushed distally the pain became progressively less severe and the agonizing expression which the patient had worn for hours was rapidly being transformed into a broad smile. The patient was unable to find words which could express the sudden and complete relief which she had just experienced. Within fifteen minutes after the passive vascular exercises had been started, the patient was entirely free from pain and her entire right leg and foot had taken on the normal pink color and she had the subjective sensation of warmth in the extremity. The foot and leg remained warm and of normal color during the entire treatment of thirty minutes. When the foot was removed from the treatment boot, the entire leg and foot quickly became ischemic again, but the pain did not return for approximately forty-five minutes. The passive vascular exercises were given at hourly intervals for periods of thirty minutes each. During the second treatment the normal color and warmth of the extremity returned after approximately three minutes.

of treatment. The progress of the development of the collateral arterial circulation can best be obtained from the drawing (fig. 5).

On the second hospital day, the patient again showed signs of

FIG. 5



Acute Arterial Embolism. Diagram showing the level of sustained arterial circulation at various intervals of time after Passive Vascular Exercise treatment was started. On the second hospital day another embolus lodged at the bifurcation of the anterior and posterior tibial arteries of the left leg. Total Passive Vascular Exercise treatment was seventy nine hours to right leg and thirty-one hours to the left leg. Patient has been well and free from symptoms since February 1934 (From Herrmann, Passive Vascular Exercises, J. B. Lippincott Company, Philadelphia, 1938.)

auricular fibrillation and when the mechanism returned to normal spontaneously that afternoon, the patient suddenly developed a pain in the left lower leg, again all the signs and symptoms of peripheral arterial embolism became apparent. Passive vascular exercise therapy was carried out within one hour after the accident had occurred and

the symptoms were relieved immediately. After a total of seventy-nine hours of passive vascular exercise treatment to the right leg, with the boot applied only from the mid-thigh distally, and a total of thirty-one hours of treatment to the left leg, the patient left the hospital without any signs of vascular insufficiency in either foot. At the time of the discharge from the hospital, there were faint pulses palpable in the peripheral arteries of the right leg but no pulses in the left leg below the knee. She received no further treatment and has remained entirely free from signs and symptoms of vascular insufficiency since February 26, 1934. Within two months after leaving the hospital, she developed a strong pulse in the internal genicular artery on both sides and a very forceful pulse in the circumflex iliac artery about the right hip. Repeated examinations have been made and we are certain that an adequate collateral arterial circulation has developed in both lower extremities. The magnitude of the collateral arterial circulation, as shown by the force of the pulses in the collateral arteries, slowly became greater for more than a year after all therapy had been discontinued.

DR HERMANN The patient here before us went through that nightmare, as she likes to think of those four weeks in the hospital, more than three years ago and, without any subsequent treatment other than digitalis therapy for her heart, she has been able to continue her work as a district nurse without interruption in order to support her three young boys. Those of you who are near can actually see the pulsations in the genicular arteries about the right knee. The pulses in the genicular arteries about the other knee are forceful and bounding to palpation. The pulse in the right circumflex artery here in the right groin is easily felt and is of excellent force. The heart action is regular at this time. This striking clinical result focused our attention on the conservative management of such major arterial accidents and our experience during the past five years with a large series of similar problems after embolism, thrombosis or trauma, has simply emphasized to us the importance of many of the so-called minor factors of importance which are so frequently overlooked by embolectomists in telling of the occasional striking benefit following embolectomy.

The symptoms of sudden arterial occlusion are extremely variable but if there is any ground for suspecting acute arterial thrombosis or

embolism we believe that the emergency treatment for acute arterial occlusion should be carried out until the correct diagnosis can be made. We are convinced that the majority of patients with sudden arterial occlusion are poorly treated. The common practice of elevating the extremity and surrounding it with hot water bottles or an

FIG. 6

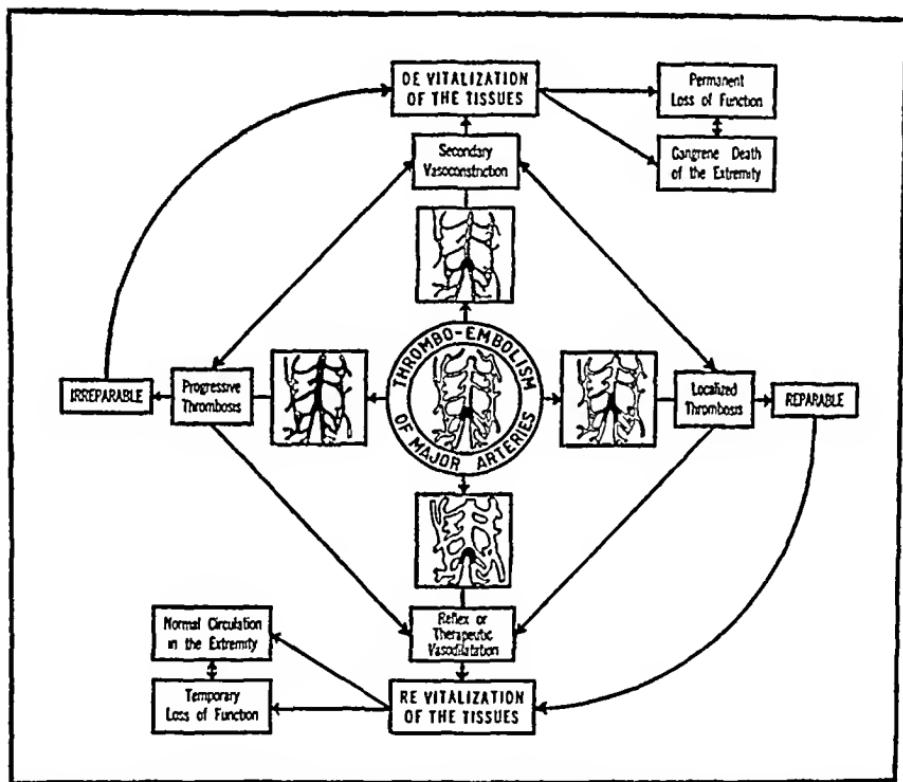


Diagram showing the various pathologico-physiologic processes which may be initiated by sudden occlusion of any major artery by embolism or thrombosis. Note that the success of therapy depends largely upon the degree of peripheral vasodilatation which is produced

electric heating pad are very bad practices. Elevation of the extremity diminishes still more the flow of arterial blood to the distal parts of the extremity and the direct application of heat frequently causes serious burns, because of the lowered vitality of the tissues. The high environmental temperature raises the local metabolism of the tissues and thus creates, as Norman Freeman has shown, a greater demand for arterial blood thereby increasing many times the deficiency in the circulation of the entire extremity.

The factor of time is of great importance and delay of just a few

hours frequently denies the patient the chance to recover without the loss of the extremity. Much depends upon the secondary changes which occur after the embolus has become fixed in the periphery or after the effects of an acute trauma to an artery have subsided. The four main groups of changes which might follow in the wake of any acute injury to a major artery can best be shown by this chart (fig 6). It can be seen that all active therapy must be directed toward the relief of the secondary vasospasm in the major arteries, as well as in the collateral arteries, if serious complications are to be avoided. If progressive thrombosis of all the connecting primary and secondary arteries occurs the process quickly becomes extremely serious and irreparable damage to the tissues of the affected extremity takes place and either permanent loss of function of the extremity or massive gangrene of the distal portions of the extremity is certain to follow.

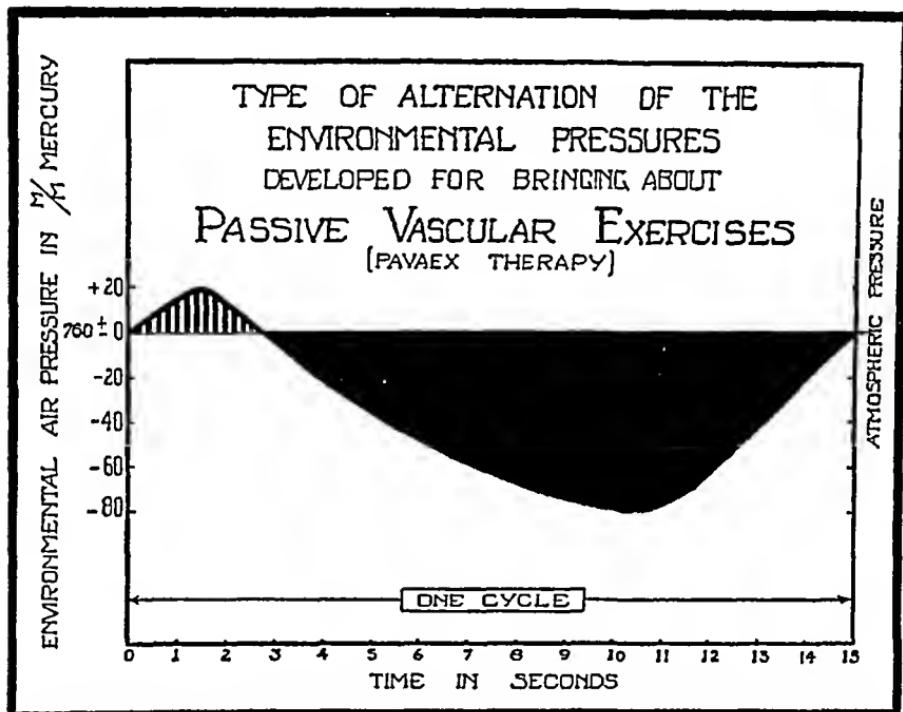
From a practical therapeutic standpoint, therefore, we are convinced that strong vasodilating drugs should be given as soon as the acute arterial occlusion is suspected or actually recognized. We have found that the intravenous injection of Papavarine hydrochloride in amounts of one-sixth grain (0.01 Gm.) to one-half grain (0.032 Gm.) acts very promptly and aids greatly in making the existing collateral arterial pathways useful and efficient. This solution should be freshly prepared from the powder and one must be certain that the drug is physiologically active. We believe that this preparation should be given to the patient in the home when the diagnosis is first made and the patient then sent to the hospital without delay. Morphine in generous amounts should be given to reduce the pain in the affected extremity. The ingestion of whisky in fairly large amounts is of distinct value since the alcohol has marked vasodilating power as well as being an anodyne.

In the hands of most general surgeons the operation of embolectomy or thrombectomy is not often successful as the slightest injury to the intima of large arteries is almost uniformly followed by further thrombosis and more extensive obliteration. Our own success with the use of the rhythmic alternation of the environmental pressure in the form of Passive Vascular Exercises (fig 7) seems to us to indicate that the conservative methods in conjunction with intensive passive vascular exercises offer the patient the greatest chance of recovery with the least risk to the patient's life and extremity. The careful

protection of the affected extremity from all types of trauma by wrapping it in cotton and keeping the skin soft and the tissues at or slightly below the average body temperature is of great importance

There is insufficient data available upon which to base an opinion concerning the practical application of the method of reflex or stasis hypoxemia of Sir Thomas Lewis as originally used by Bettmann in 1930 and recently reintroduced by Collens and Willensky. We be-

FIG. 7



Kymographic record of the pressure changes characteristic of Passive Vascular Exercises. Note the gradual rise and fall in cyclic sequence with the pressure predominantly in the phase below the existing atmospheric pressure (From Herrmann, J A M A , 1935)

lieve that in cases of acute arterial occlusion the stasis of venous blood in the tissues is harmful and frequently leads to secondary thrombosis of the progressive type and subsequent devitalization of the tissues of the affected extremity

We are confident that the appearance of cyanosis, due to capillary paralysis, after any acute arterial occlusion is a grave sign and every effort should be made to free the extremity of the static blood before further efforts to increase the flow of arterial blood to the extremity

are begun Dr Reid has, for many years, advocated the very gentle superficial massaging of this static venous blood back toward the heart. In this way the cyanosis and congestion can frequently be "milked" out of the extremity with amazing rapidity. The continuation of the passive vascular exercises when the extremity is once cyanotic or becomes cyanotic during the treatment, is useless and may even be harmful. Unless the distal parts of the extremity can be made to remain pink or light red in color, all mechanical means, except light massage, of promoting a more efficient arterial circulation will be of little permanent value.

From this discussion you can see that much good can be done in a very simple way if the process is recognized early and the active treatment begun before disintegration of the tissues has already started, or until extensive or progressive thrombosis has blocked those pathways which might have been made useful in the establishment of an efficient collateral arterial circulation. Remember that elevation of the extremity and the local application of heat are extremely dangerous in all patients with arterial insufficiency in the extremities.

In clinical practice we also see other varieties of sudden occlusion of major arteries especially those resulting from the surgical ligation of a major peripheral artery because of sudden rupture of the coats of the artery from trauma or disease. The sharp edge of a fractured bone may sever a major artery or syphilitic disease of the wall may weaken it sufficiently to permit a large arterial aneurysm to develop. Atheromatous plaques may also weaken the wall and permit aneurysmal dilatation to occur. When such aneurysms become large and the wall becomes extremely thin the danger of sudden rupture and sudden death are so great that ligation of the major branches to and from the aneurysm must be done. We are, therefore, frequently faced with the problem of overcoming the acute arterial insufficiency which results from the surgical ligation of the major arteries to an extremity. In otherwise healthy young men and women the danger of gangrene resulting from such a procedure is considerably less than in the elderly arteriosclerotic patient. In view of the importance of this problem in general practice I should like to have Dr McCandless present the story and physical findings on this elderly woman for your consideration.

FALSE ANEURYSM OF FEMORAL ARTERY

DR HARVEY G McCANDLESS This patient, a white woman of seventy-four years of age, was brought into the hospital in a confused state of mind but apparently in great pain which she localized in the region of a large pulsating mass in the upper anterior portion of the left thigh. This mass first became noticeable about one week before admission to the hospital and had steadily grown larger in spite of local treatment. On the morning of the day of admission to the hospital the patient complained of a sharp severe pain in the left groin and her physician noticed that the mass in the groin became much larger and began to show some bluish discoloration. The pain was so severe that morphine was necessary for relief. From the patient's daughter we obtained the information that the patient fell down some stairs and sustained a severe "bruise" in the left groin from the handle of a broom. This accident happened about five months before any swelling in the upper portion of that thigh was noted by the patient. Physical examination showed an elderly woman who was obviously in great pain. Study of the peripheral arterial circulation showed evidence of peripheral arteriosclerosis of a moderate degree. Blood pressure in the left arm was systolic 200, diastolic 115. Her temperature was 99° F and her pulse rate was 110 per minute. The pulse in the radial artery was bounding and there were numerous extra-systoles present. Examination of the left thigh disclosed a large pulsating mass about four inches wide and about six inches long. The skin over the mass was discolored and palpation revealed considerable induration in the muscle for a short distance beyond its limits. The skin was freely movable over the mass and all the peripheral pulses were of fair quality. It was obvious that this was a dissecting aneurysm and a traumatic rupture of the left femoral artery. The fact that it had been growing larger very rapidly during the day prior to admission to the hospital made the family physician certain that surgical intervention was absolutely necessary, with which we agreed. As an emergency procedure, therefore, the common femoral artery above the aneurysmal dilatation was isolated and tied with cotton binding tape about one-fourth inch wide. The artery was tied in continuity. The pulsation in the mass ceased immediately after the common femoral artery was tied. The femoral artery below the aneurysm

was not ligated in this case. On the following morning there were unmistakable signs of serious arterial insufficiency in the distal part of the left leg and in the left foot. Pain had left the upper portion of the thigh and was now very severe in the foot and in the toes. The arterial insufficiency continued to become more acute and the increase in the pain was evidence that spontaneous recovery was very improbable.

DR HERRMANN I should like to interrupt Dr McCandless at this point just to emphasize the fact that in elderly people the reestablishment of the arterial circulation does not usually take place with the same facility that it does in very young subjects. The fact that Dr McCandless found evidence of marked arteriosclerosis in the other peripheral arteries must be kept in mind. All measures which promote peripheral vasodilatation should be resorted to early in such a case and, as we explained in the discussion of the preceding case, it is wise to give Papaverine hydrochloride ($\frac{1}{6}$ to $\frac{1}{2}$ gr) intravenously when the first signs of such an acute arterial insufficiency develops. Such a patient should also be given whisky in fairly large doses to promote as much peripheral vasodilatation as possible. Heat should *NOT* be applied to such an extremity under any circumstances. The immersion of the fore-arms and hands in water at 42°C is a simple way of producing vasodilatation in the lower extremities. In addition to all of these measures we believe that such a patient should also be given the benefit of the mechanical stimulation of the flow of blood through the collateral arterial pathways by Passive Vascular Exercises. Let us now hear from Dr McCandless about the subsequent course of this patient in the hospital and at home.

DR McCANDLESS In this case all measures which tend to promote peripheral vasodilatation were resorted to at once and since we have the apparatus (fig. 10) for the production of passive vascular exercises constantly ready for use we lost no time in taking advantage of this important means of overcoming arterial insufficiency of this type. After the first five hours of passive vascular exercise treatment, used in conjunction with the other vasodilating substances, there was a great improvement in the color of the foot and leg and the pain had completely disappeared. This treatment was continued intensively for six hours each day for three more days at which time the pink color remained and the foot remained fairly warm. The postoperative

course was uneventful except for some fever on the seventh post-operative day which was due to pulmonary atelectasis. The wound healed by first intention. The pulsation in the mass never returned and the collateral circulation in the left leg developed sufficiently to permit ordinary activity without symptoms. We are presenting her at this clinic today to show that even at the age of seventy-four years the serious complications of the sudden abstraction of the required amount of blood from an extremity can be successfully treated in a truly conservative way.

DR. HERRMANN: I can certainly corroborate what Dr. McCandless has just told you. We should always strive to accomplish a satisfactory clinical result in the simplest manner. I am sure the conservative surgeon or internist has much to offer this great group of patients who for one reason or another develop an occlusion of some major peripheral artery. From our experience with a large series of these patients we are convinced that amputation of the part should only be resorted to after all the conservative methods of treatment have failed to bring about relief, and the extremity has actually undergone disintegration.

The problem of the management of arteriovenous aneurysms is beyond the scope of this clinic, consequently, I shall omit all references to such disturbances at this time.

THROMBO-ANGITIS OBLITERANS (BUERGER'S DISEASE)

The routine examination of all peripheral arteries would result in a much earlier diagnosis of organic arterial diseases and the true nature of a disease which has erroneously been treated for weeks, months or even years, as fallen arches, rheumatism or sprained ankles, would thus be established. If in addition we were to make a practice of counting the rate of the heart by palpation of the pulse in the dorsalis pedis artery rather than in the radial artery, many more cases of early vascular disease would be detected. Surgeons are becoming more conservative as the clinical course of the various types of organic arterial disease is being made known to them and in most clinics every effort is being made to prevent the amputation of extremities whenever it is possible.

In every large community there are thousands of people who are unaware of the fact that their major peripheral arteries have been

occluded by some disease process because they have had very few signs to indicate that they have a very narrow margin of safety in regard to the arterial supply to the extremities. From our own study of a large series of such patients we have come to the conclusion that the majority of the serious complications of organic arterial disease actually result from the speeding up of the usual slow occlusion of the major and secondary arteries, or from exposure to some mechanical, thermal or chemical trauma. Such trauma not only throws an added strain on the already overburdened collateral arteries but it also induces a high grade secondary vasospasm in all of the arteries of the affected extremity. This more or less sudden demand on the collateral arteries with the superimposed vasospasm of varying intensity will, most certainly, give rise to severe pain, and gangrene will usually result, unless the patient or his doctor can do something to tide the tissues of the extremity over this period of acute arterial insufficiency. Periods of acute ischemia of the tissues of an extremity frequently appear in the course of true thrombo-angiitis obliterans, consequently patients with such a pathologic process involving the peripheral arteries should be given the benefit of all conservative methods of treatment before amputation of the extremity or extremities is seriously considered. In order to bring out the important factors in the diagnosis and treatment of this disease entity I shall ask Dr. McGrath to present to us a typical case of thrombo-angiitis obliterans.

DR. EDWARD J. MCGRATH: This patient, a white male, forty-one years of age, was admitted to the hospital because of swelling and redness of the right great toe associated with intense pain in the entire foot and ankle. The great toe has been deep cherry-red in color for some weeks, and about one week before admission to the hospital the patient tried to dig out an "ingrown nail". Following this the toe became greatly swollen and intensely painful.

The patient is of Irish-Danish descent and has lived in the United States all of his life except for the eighteen months he spent in France during the World War. His dietary habits have been nothing unusual although on questioning he states he ate heavily of French "black bread" during the war. He has been a heavy smoker of cigarettes (about forty cigarettes per day) since he was about twenty years of age. There is no family history of any similar ailment. There is no history of frostbite of the feet but he states that he was

exposed to dampness and wet feet during his military service. His present illness began about ten years ago when he noticed small areas of inflammation "under the skin" of the lower legs. These areas would remain sore for about a week or so and then spontaneously disappear. At about this same time he complained that his feet were cold most of the time and that he frequently experienced a vague aching pain in both feet at the end of the day. After a year or so the pain came on more frequently and was more severe. At times the pain would be so severe that he would have to sit with his legs hanging over the side of the bed to get any relief. In this position the feet would become greatly congested with blood and take on a cherry-red color. Gentle massage of the dorsum of the feet seemed to give him some relief from the aching pain. About this same time he began to notice cramp-like pains in the calf muscles of both legs after slight exertion. This cramp-like pain would promptly disappear if he would stop walking only to reappear after further exertion of the same degree. This typical intermittent claudication has steadily gotten worse so at the present time even slight exertion or walking brings on the pain. There has been some coldness and numbness of the fingers during the past five years but these complaints have not been present constantly.

The entire physical examination was normal except for the extremities. All laboratory and special tests failed to show any abnormality. The blood Wassermann reaction was negative. Roentgenograms of the feet showed slight diffuse loss of calcium in the bones.

Examination of the hands showed that the index finger of each hand was shortened, pointed and the skin was white and glossy. There were no ulcerative lesions present. Both hands were objectively cold. There was moderate bilateral hallux valgus. The right great toe was dusky-red to purple in color with the discoloration most marked on the medial aspect. There was an ulcerated area at the medial border of the nail from which exuded a small amount of seropurulent material. The feet and legs were objectively cold. There were no pulses palpable in the dorsalis pedis artery or in the posterior tibial artery of either foot. A faint pulse could be felt in each of the popliteal arteries and the pulse in the femoral arteries at Poupart's ligaments was of good quality. Special studies of the peripheral arterial system showed a fairly marked degree of arteriolar obliteration.

tion, especially in the right foot with superimposed secondary vasospasm to contribute to the vascular deficiency in the lower extremities. The arterial deficiency in the upper extremities was due almost entirely to arteriolar spasm. Cultures of the ulcerated area showed some diphtheroid bacilli together with non-hemolytic *staphylococcus aureus* micro-organisms.

DR. HERRMANN This is a classical clinical story for thrombo-angitis obliterans. It is now well established that this disease is not limited to the central European Hebrews and authentic reports show that it occurs in almost all parts of the world and among the males of all races. The relative predominance among Russian Jews remains unexplained. Recently Yater of Washington described the disease in full-blooded negroes. Why the disease does not occur more frequently in that race or among women has never been satisfactorily explained.

The long history of vague pains in the legs and feet following the attacks of migrating phlebitis in a young male should lead you to suspect the presence of this form of inflammatory angitis. The subsequent vasomotor phenomena of blanching, followed by congestion and the story of long standing intermittent claudication together with the present picture of a swollen, cherry-red toe which causes excruciating "rest" pain is certainly sufficient evidence upon which to base the diagnosis of clinical thrombo-angitis obliterans. The fact that he has been a heavy smoker greatly adds to his burden and makes recovery or even improvement very improbable until he abstains from the use of tobacco in all forms. There is, however, no absolute evidence that the alkaloids of tobacco are the sole or even the most important etiologic factor of this disease. There are many other alkaloids which have a similar action upon the peripheral vascular system, namely, the derivatives of ergot and all of the abnormal protein molecules which possess an ergot-like or a nicotine-like action. These last mentioned substances are formed within the human body under certain conditions so it is possible that the main etiologic factor is actually manufactured within the body of the patient and is only aggravated by these other extrinsic substances. There is, likewise, some evidence that a disturbance in the choline metabolism of the individual might play a rôle in the causation of this disease process. In the last analysis the essential pathologic process in the peripheral arteries, veins and

nerves appears to be of an inflammatory nature, but whether it is of the bacterial or chemical variety has not yet been settled

Since the true etiology or even the true nature of this malady is still unknown all our therapy must be symptomatic or empirical in nature. The course of the disease is so varied that one must be extremely careful not to put too much stress upon the therapeutic procedure which was being employed at the time the improvement took place. Certainly our first and foremost step must be directed toward removing all substances which might further depress the peripheral arterial circulation. It has been amply proved that these patients are extremely sensitive to tobacco and all its alkaloids, consequently, the complete abstinence from the use of tobacco must be impressed upon the patient from the very beginning. Likewise all ergot and ergot derivatives must be avoided. Putrefaction in the intestinal tract should be overcome to guard against the formation of the abnormal protein molecules with the nicotine-like and ergot-like action. The next important problem concerns the hygiene of the feet and the prevention of mechanical, thermal and chemical trauma to the skin of the extremities. The following general directions for the care of the feet must be followed by all patients who present arterial insufficiency due to organic disease of the arteries of the extremities.

GENERAL DIRECTIONS FOR THE CARE OF THE FEET

- 1 Wash feet each night with neutral (face) soap and warm water
- 2 Dry feet with a clean soft rag *without* rubbing the skin
- 3 Apply rubbing alcohol (70 per cent) and allow the feet to dry thoroughly, then apply a liberal amount of vaseline or toilet lanolin and gently massage the skin of the feet
- 4 Always keep your feet WARM. Use woolen socks in the winter and white cotton socks in warm weather. Use a clean pair of socks each day
- 5 Use loose fitting bed socks instead of hot water bottles, electric heaters or any other form of mechanical heating devices
- 6 Wear properly fitting shoes and be particularly careful that they are not too tight. Use soft leather shoes without box toes
- 7 Cut your toe nails only in good light and only after your feet have been cleansed thoroughly. Cut the toe nails straight across
- 8 Do not cut your corns or calluses
- 9 Do not wear circular garters
- 10 Do not sit with your legs crossed
- 11 Do not use strong antiseptic drugs on your feet. Never use Tincture of Iodine, Lysol, Cresol or Carbolic Acid
- 12 Go to your doctor at the first signs of a blister, infection of the toes, ingrowing toe nail or trouble with bunions, corns or calluses

- 13 Drink at least four quarts of water each day
- 14 Eat plenty of green vegetables and fruit in an otherwise well balanced, liberal diet, unless you have been ordered to follow some special diet
- 15 Do not use tobacco in any form
- 16 Have a member of your family inspect your feet at least once a week
- 17 Carry out the Active Vascular Exercises as they were taught to you Do them regularly and faithfully for the prescribed time each day

The position of the resting extremity which affords the best exchange of arterial and venous blood, should be determined during the first examination of any patient who shows objective evidence of some peripheral vascular disturbance Ordinarily this position of "Optimum Resting Level" is between three and six inches *below* the level of the heart When this optimum position is found, the superficial veins will be carrying a quantity of blood which neither distends nor retracts the skin which overlies them The improvement in the circulation which can be brought about by graded amounts of active exercises, whenever infection and gangrene are not present, is not difficult to demonstrate to the patient, consequently the Buerger-Allen Active Vascular Exercises should be an important part of therapy Patients with thrombo-angiitis obliterans have been shown to have an increased viscosity of the blood and because of this the intravenous injection of saline solution (150 to 300 cc of a 3 or 5 per cent NaCl solution) is frequently resorted to in the active therapy of this disease There is, however, no evidence to show that there is any specific action of the salt solution in these patients and for that reason many of the clinics throughout the country advise their patients to drink large quantities of water in order to decrease the viscosity of the blood Foci of infection should be eradicated in spite of the fact that no direct connection between chronic infection and this disease entity has been found The vasodilating drugs of the theophyllin group are usually ineffective, while acetylcholine hydrochloride is quite toxic when given in large doses Mecholyl has been shown to be an effective peripheral vasodilator but from our own experience the oral administration of alcohol in the form of whisky is still the most effective vasodilating substance of this group The use of various tissue extracts has brought about improvement in some cases The use of typhoid vaccine intravenously to produce protein shock and high fever is a common form of therapy The initial dose of the ordi-

nary TAB vaccine should be from fifteen to thirty millions of organisms. These injections are given every other day for a course of twelve or eighteen injections after which a period of rest of one month is given. Usually the dose is increased by twenty-five millions of organisms each time and as many as 500 millions have been given in a single dose toward the end of the treatment.

The element of vasospasm is considerable in some of these patients and on that basis many surgeons have suggested sympathectomy as the ideal treatment for this disease. Experience on the other hand has failed to bear out that assumption and it is our belief and the opinion of many of the surgeons who are interested in this disease, that operations upon the sympathetic nervous system do not bring about anything which can not be brought about by much simpler means. When there is evidence of extensive organic arterial disease in the extremities I believe that such operations are really contraindicated.

On the basis of the experimental work of Dr. McGrath and on the basis that the disease rarely attacks the female, we have been injecting into the hip muscles rather large doses of theelin in oil (2000 to 5000 units) about every seven or eight days for a period of several months with the hope that some protective action would result. Our series of patients is still too small to permit us to draw any conclusions from the clinical experiment. Certainly it does not cause any known harm in these males and does seem to give them relief from the clinical standpoint. We have also given Sulfanilamide (Piontosil) intravenously in doses of 20 cc twice daily for several weeks with apparently some improvement.

When pain is uncontrollable by medicinal means we employ the method of Smithwick and White for the desensitization of the foot by crushing the peripheral sensory nerves at a point about five inches above the ankle. This gives relief in the majority of the cases if the inflammatory neuritis has not already ascended to some higher level.

When there are painful ulcers on the toes or foot they are carefully cleansed and all necrotic tissue removed. Care must be taken not to cut out any tissue which is not grossly necrotic as these wounds are hypersensitive and mechanical trauma to the wound frequently causes the process to spread or become more painful. The local application of some anesthetizing ointment, such as nupercainal ointment, frequently is effective in controlling the pain. As a rule we keep all such

lesions dry by applying an aqueous solution of Gentian Violet (5 per cent) or an aqueous solution of mercurochrome (5 per cent) to the lesion several times each day.

All of the therapy which has been mentioned must be considered as symptomatic and not primarily directed toward overcoming the peripheral arterial insufficiency in any active way. It is well known that there is usually a well developed collateral arterial circulation in these patients possibly due to the slowness of the obliterating process which has been acting upon the secondary arteries of such extremities for such a long time. The really discouraging fact, however, is that the inflammatory process in the vessels is usually a progressive one and the collateral arteries which are developed in any way are soon obliterated by this extension of the original inflammatory process.

In the early stages of thrombo-angiitis obliterans when vasospasm is pronounced, we have found that passive vascular exercises with local hyperthermia is of distinct value in overcoming the arterial insufficiency in the distal portions of the extremities, but after the obliterating process has once extended to the smaller arteries and arterioles, as is the case in the later stages of the disease, then mechanical stimulation of the flow of blood through the collateral arterial pathways is only of temporary value and hardly justifies the time, expense or the effort necessary to give the patient adequate and intensive therapy of this kind. The results following passive vascular exercise therapy in the late stages of thrombo-angiitis obliterans are not very encouraging.

DR. MCGRATH: The various types of treatment which Dr. Herrmann has just outlined to you have all been carried out on this patient during the past five months. It is, of course, impossible to say which one, which combination, or even if any of the things which have been done should be considered responsible for the striking improvement which you see has taken place in this patient. He has stopped smoking, he has been taught how to care for the skin of his feet, he has had a total of about 200 hours of passive vascular exercise therapy with mild local hyperthermia, and he has had a course of each of the medicaments which have just been outlined to you. It may seem strange to you why so much has been done at one time but if you could only picture the physical, as well as, the mental condition of this patient five months ago when he was in great agony and begging

to have his leg amputated, you will understand why he was given the benefit of every reasonable means of halting the process and overcoming the pain. He is free from pain and the gangrenous process of the toe has separated nicely and the base is almost healed. We cannot, of course, give this man any assurance that the process will not become active again but we do feel that if he continues to follow out a régime such as Dr Herrmann has outlined for him, the chances of further complications will be reduced to the minimum.

ARTERIOSCLEROSIS OBLITERANS

Sufferers from arteriosclerotic peripheral vascular disease constitute a much neglected group of patients when compared with those suffering from the other forms of peripheral vascular disorders which have received so much attention during the past decade. Arteriosclerosis is responsible for the vast majority of disturbances of the peripheral arterial circulation, and it has been assigned as the etiological factor in three out of every four patients admitted to our Vascular Disease Clinics. The economic loss which results from the disabilities brought about by this degenerative process is very large when we consider the total cost to charitable organizations and to the State when, following amputation of an extremity, its sufferers have ceased to be objects of interest to the medical profession. Our own statistics, as well as the statistics of several other large charity clinics in this country, show that only about 20 per cent of the patients who lose an extremity because of gangrene ever become rehabilitated by the use of artificial legs. This fact alone should make us exhaust the possibilities of all conservative methods of treatment before we consider some major amputation. The manifestations of arteriosclerotic peripheral vascular disease vary so much that it is difficult to find one patient who presents all of the important features for our discussion. I shall ask Dr Fan to tell you about our last patient who presents many of the important points which I wish to emphasize to you.

DR FAN This patient, a white male of sixty-four years of age, was admitted to the hospital because his left foot was greatly swollen and reddened and the toes were gangrenous and covered with a foul smelling purulent exudate. There were several "red streaks" on the leg and thigh along the course of the great saphenous vein. The toes

FIG 8



Photograph showing the extent of the trophic lesions of the feet after the acute cellulitis was made to subside by the judicious use of warm moist dressings applied to the leg only

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of the right foot were discolored and a dark colored blister covered the plantar surface of the great toe. The patient states that a similar blister appeared on the great toe of the left foot about four months before admission to the hospital. This blister gradually grew larger and larger and soon the entire toe was black and the patient began to have constant aching pain in all of the toes of that foot. A large ulcer soon formed and continued to spread until, at the time of admission, the process had spread to the plantar surface of the foot. His feet have been numb and cold for the past year or so, and he had noticed cramps in the muscles of the calf on slight exertion. He was told that he had sugar in his urine twelve years ago, but he was never given any instructions concerning his diet and he has not had any insulin to control the glycosuria.

At the time of admission to the hospital he had been having "chills and fever" and shortly after admission he had one of his severe chills. His oral temperature was 104° F., his pulse rate about 100 per minute and the respiratory rate was about 24 per minute. The white blood cell count was 9,000 and the urine was loaded with sugar, acetone, diacetic acid and a slight trace of albumin. Blood sugar was 200 mg per cent and the CO₂ combining power was 52 volumes per cent.

Examination of the peripheral arterial system showed complete occlusion of the major arteries below the left knee and marked sclerosis of the arteries of the right lower leg with high grade arterial insufficiency in both feet. The photograph (fig. 8) shows the condition of the feet after the acute cellulitis was made to subside with warm moist saline dressings applied constantly for about five days. Absolute bed rest with the extremities placed at the level of optimum circulation was carried out, after careful cleansing of the foot with removal of the grossly necrotic tissue had been done to insure adequate surgical drainage of the infectious process in the foot. The oral and intravenous administration of moderately large quantities of fluid (total of about 3000 cc per day) were kept up during the acute phase of this patient's illness. The diabetes was kept under fair control by a dietary regime together with moderately large doses of insulin.

DR. HERMANN: I should like to interrupt Dr. Fan at this point since the care of the diabetes is such an important problem to you who must handle these cases in your private practice. We are extremely

fortunate in our clinic since we have a physician trained in the care of diabetes with us at all times, so I shall take the liberty of asking our medical consultant, Dr. Louis B. Owens, to give us more detailed information concerning the care of such a diabetic person as the one Dr. Fan has just told us about.

DR. OWENS The medical treatment of the diabetic who is suffering from some acute infectious process or gangrene is of great importance. The management of so-called "surgical diabetes" is always more difficult and requires much more careful planning of the diet and the dosage of insulin. An adequate diet is essential and if the patient is unable to take food by mouth, the food, in the form of solutions of glucose and the salts, must be given by the intravenous route. As a rule, however, these patients are not so acutely ill and frequently are quite anxious to take food by mouth. Most of these patients were formerly mild diabetics but the added demands brought about by the acute infection or gangrene make them decidedly worse and in some cases they become absolutely uncontrollable by the ordinary measures. The diet in all of these cases should be adequate and the carbohydrate content should not be too low. We believe that it should be around 110 to 140 Gm for the average patient. The remainder of the diet can be made up of about one gram of protein for each kilogram (2.2 pounds) of body weight and the fat content of the diet between 90 and 100 Gm if the patient is not obese.

The patient just presented was given a diet consisting of 140 grams of carbohydrate, 70 Gm of protein and 70 Gm of fat. During the first few days it was necessary to give the patient as much as 105 units of insulin, in three unequally divided doses (45-35-25 units before each meal) to get the urine free of sugar. It is desirable to keep the urine free of sugar at all times if that is possible. The level of the blood sugar is not so important and it is not necessary nor even wise to make any great effort to keep the blood sugar level within the normally accepted limits of 80 to 120 mg per cent. Most of the arteriosclerotic patients have a moderately elevated blood sugar and are usually uncomfortable if that high level is reduced any appreciable degree. The really important consideration in these elderly patients is to keep the urine free of sugar. Insulin is usually necessary in the management of the acute surgical problems which come on in the diabetic. As a rule when the problem is not an emergency one,

a dose of five to ten units of insulin is given before breakfast and again before supper, and, then according to the degree of glycosuria, the various doses are increased until the patient's urine is free of sugar. Usually a noon dose of an equal number of units of insulin is necessary to accomplish the desired result. Very soon after the urine becomes free of sugar, as a result of the dietary and insulin treatment of the diabetes and the proper surgical management of the infection or gangrene, it is frequently possible to reduce the amount of insulin to a fraction of what it was originally. In this patient the superficial infection and acute lymphangitis soon subsided, but the gangrene continued to spread in the left foot. The pain was excruciating, consequently, surgical removal of the extremity was carried out under spinal anesthesia. Immediately there was a great improvement in the diabetes and within one day it was possible to keep the patient's urine sugar free on the same diet with only 35 units of insulin for the twenty-four hours. A patient who shows such improvement very soon demands more to eat and it is usually possible to increase the content of the diet without altering the amount of insulin which the patient was receiving. Two weeks after this patient's left leg was removed we were able to increase the diet to 160 Gm of carbohydrate, 80 Gm of protein and 100 Gm of fat. Now he is a relatively mild diabetic and, from the improvement which has resulted from the treatment of the beginning gangrene of the toes of the remaining foot, I am sure he will continue to show improvement in his ability to handle carbohydrates without showing glycosuria. I wish to emphasize that whenever possible you should attempt to keep these arteriosclerotic patients in proper balance by dietary measures alone and insulin therapy should be added only when some surgical complication makes the simple dietary regime inadequate to prevent glycosuria.

DR. HERRMANN Dr. Owens has given us a very clear and concise statement of the problems in the "surgical diabetic" as contrasted with the ordinary variety of diabetes. Active cooperation between the internist and the surgeon must exist at all times. From the surgical standpoint this patient was given excellent care to the skin of his remaining foot and every ordinary means of promoting a better arterial circulation was resorted to as soon as he recovered sufficiently from the effects of the supracondylar amputation of the left leg.

(fig 9) Heat of more than body temperature must be avoided in the management of these complications, except when acute lymphangitis is superimposed upon a gangrenous process. The benefits which would be derived from the local application of warm, moist dressings to the *leg* of the affected side, however, would greatly overshadow the damage which such dressings might bring about by raising the local metabolism of the tissues.

FIG. 9

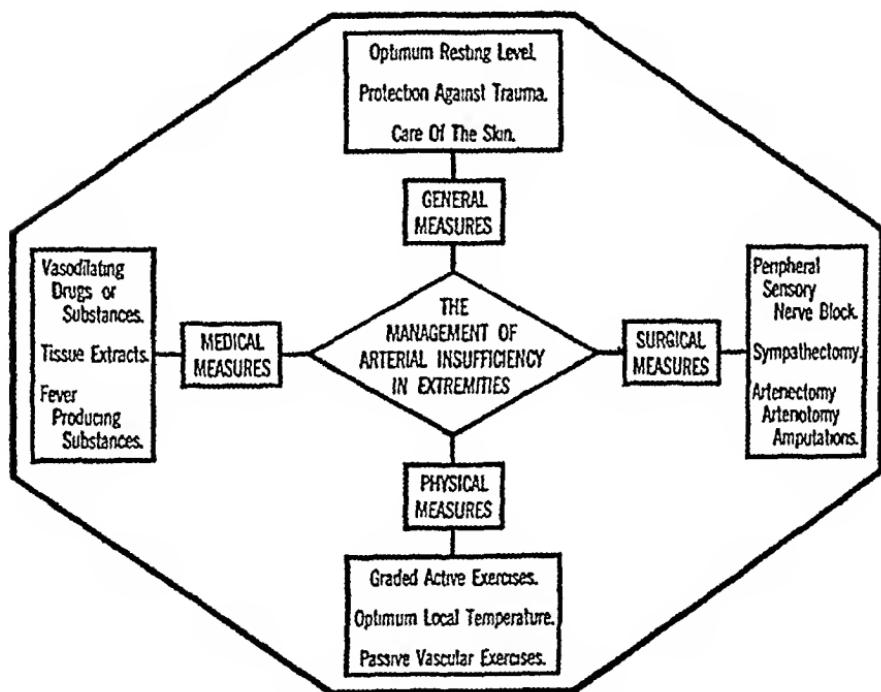


Diagram showing the therapeutic measures of importance in the management of arterial insufficiency in the extremities.

It is far better to leave the patient untreated than to add to the patient's already great burden by advising either the elevation of the extremity or the local application of heat. We have observed many patients with high grade arterial insufficiency in an extremity who would have recovered had it not been for the ill-advised application of a hot water bottle and the resulting burn on the toes.

The gangrenous foot should be next covered with a dry dressing and the local heat should *not* be applied to the foot. Conservative therapy was certainly not indicated in the left leg, except to control

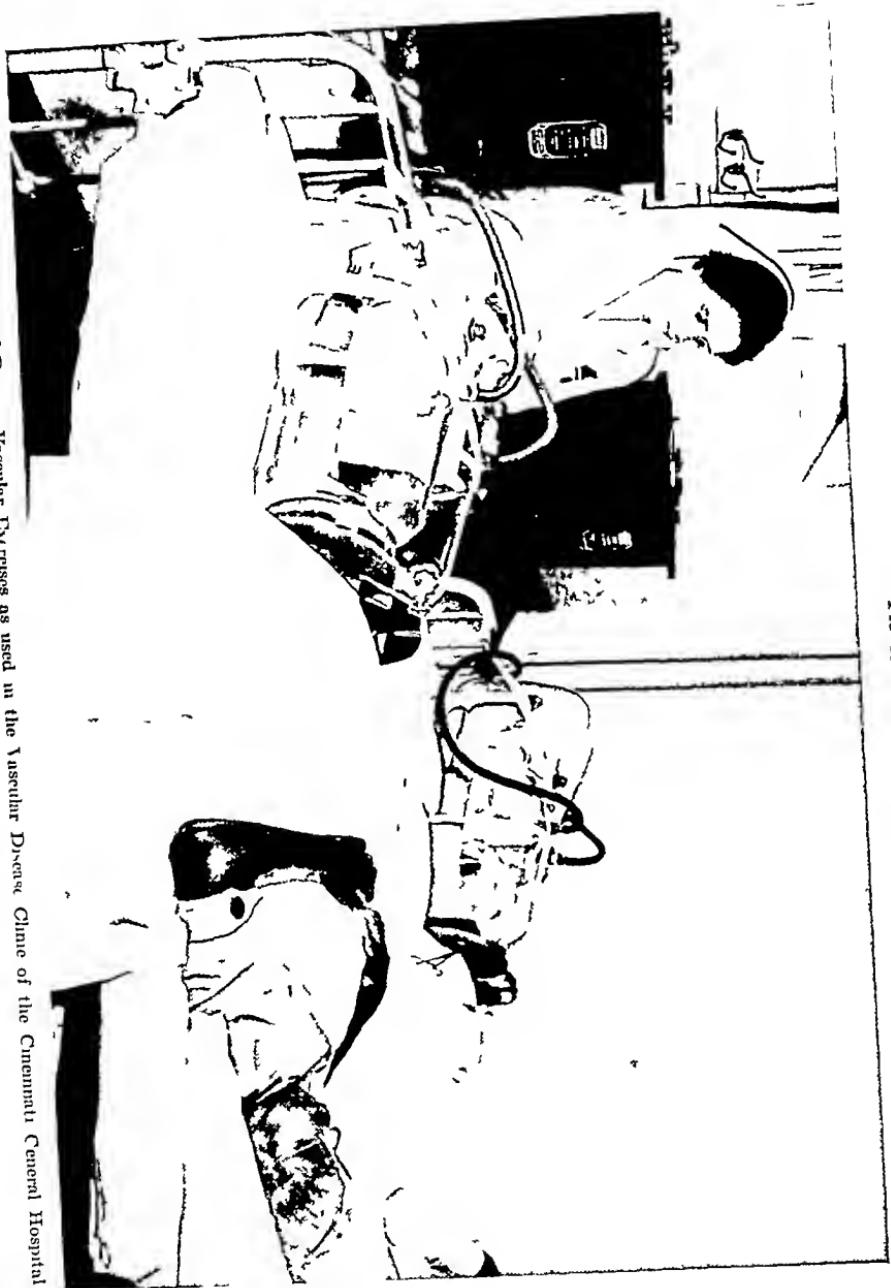
the acute lymphangitis, and all efforts to save tissue were directed to the right foot in which signs of gangrene had already made their appearance. In the presence of any acute inflammatory process, which has been superimposed upon gangrene due to circulatory insufficiency, the use of the mechanical means of stimulating the flow of blood through the collateral arteries must be considered dangerous. The trophic lesions on the right foot showed no evidence of inflammation, consequently, intensive Passive Vascular Exercises were started within four days after the left leg had been removed by amputation. The entire right foot soon became warm and normal in color. The dark, mummified areas on the tips of the toes gradually began to separate. He received a total of 240 hours of Passive Vascular Exercise treatment to the right leg during the following three months. At present you can all see that the tips of the toes are well healed and the foot is warm and of good color. There has been no pain in this foot for the past two and one-half months. He is able to bear weight on this foot without discomfort and I feel it is fair to conclude that the stimulation of the flow of blood through the collateral arterial pathways has aided materially in the reestablishment of a circulatory balance in this extremity. In our clinics this type of process is fairly common, and it is because of the distinct subjective, as well as, objective improvement which results so frequently from the Passive Vascular Exercise therapy (fig. 10) in such patients that we are convinced that it should be seriously considered when such a clinical problem as this one is presented to you. It is relatively simple to remove both legs, but let us not forget for even a minute that few of us would want to meet such a fate. It is our duty to try to conserve tissue whenever possible if it can be done without undue risk to the patient's life. Certainly you can see by the expression on this patient's face that he is most grateful for having been spared the mental agony of the loss of both legs.

In concluding this clinic I wish to emphasize once again that the majority of the peripheral vascular disturbances are serious problems to deal with and they actually account for an unbelievable amount of suffering and disability and even contribute, indirectly at least, to a great annual loss of life throughout the world. We must constantly guard against overenthusiasm, as well as, unwarranted pessimism, for much patience, keen clinical judgment and constant attention to the

"petty details" of treatment are usually necessary if the physician expects to carry a patient through one of these phases of acute arterial insufficiency without having some serious complication shatter all his hopes for success

As I intimated at the beginning of this clinic, the prevention of many of the catastrophes of peripheral vascular diseases is a great but sadly neglected duty of doctors. If, in the course of routine physical examinations, patients who have impaired peripheral arterial circulation were advised to adopt those measures which will get rid of calluses and corns and put the skin of the feet in the best possible condition, an incalculable amount of suffering could be avoided in such a simple way. If those "petty details" of care which have been constantly advocated by Mont Reid, Arthur Allen and others, receive the patient's undivided attention and the careful supervision of the physician, the task of the surgeon will be lightened and many fewer sacrifices will have to be placed at the altar of gangrene.

FIG 10



Apparatus for the production of Passive Vascular Exercises as used in the Vascular Disease Clinic of the Cincinnati General Hospital

Diseases of Endocrine Glands

SOME OF THE ATYPICAL MANIFESTATIONS OF HYPERTHYROIDISM WHICH OBSCURE ITS DIAGNOSIS WITH OBSERVATIONS ON SOME OF THE CARDIAC FEATURES OF THIS CONDITION*

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THERE are few conditions in which a correct and early diagnosis is more important than hyperthyroidism, if uncared for, it may produce incalculable harm, if promptly and properly treated, it may be cured. The diagnosis of typical hyperthyroidism is relatively easy. Under certain circumstances, however, its existence is not always easily recognized. When this is the case, hyperthyroidism may be said to be "masked".¹ This term is a good one, for it tersely expresses the fact that the existence of hyperthyroidism may be hidden and its recognition obscured.

ATYPICAL AND MASKED HYPERTHYROIDISM

We wish this afternoon to present several cases which are in our opinion good examples of this and also to discuss certain cardiac features which they present. In the first three cases that we will show, the presence of hyperthyroidism is obscured, either because its manifestations are atypical in the sense that some or all of the features that we expect are absent or poorly developed, or because the features of hyperthyroidism *per se* are overshadowed by some second-

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ary result, particularly heart failure, which was present in one form or another in all of the cases we will show today

Low-Grade Hyperthyroidism — The degree of thyroid over-activity is not necessarily constant or fixed but may spontaneously increase or decrease. Apparently, there is a small group in which the metabolism as measured by the basal metabolic rate constantly fluctuates around a top-normal figure for a long period of time. It is probably never much above and never below the upper limits, as a result the common symptoms of hyperthyroidism are never strikingly shown. The long-continued, though slightly elevated, metabolism may, however, ultimately affect the heart deleteriously. The first case we will show we believe to illustrate this type of thyrotoxicosis.

CASE 1 — J. C., white, aged fifty three, has been under the care of the Medical Clinic of another hospital since 1928. His history indicates that in 1919, he had his first paroxysm of rapid irregular heart action. Similar attacks recurred approximately once a month and lasted at first no more than a few hours. By 1928, the attacks had become more frequent and had lasted as long as two days. Aside from slight breathlessness, they caused him no trouble, and between attacks, he was apparently perfectly well. The paroxysmal disturbances were almost certainly auricular fibrillation, for soon after coming under observation in 1928, this arrhythmia became permanently established.

No cause for this disturbance could at first be found. In the many observations made between 1928 and today, no definite cardiac enlargement and no evidence of congestive failure has been demonstrated. No murmurs were ever heard, the blood pressure was always normal, ranging between systolic 130, diastolic 80 and systolic 110, diastolic 72, the Wassermann was normal, and there was nothing notably progressive in his heart condition, even now, his only complaint is moderate breathlessness on exertion. These facts opposed a rheumatic, luetic, hypertensive, or arteriosclerotic etiology. Hyperthyroidism was originally considered but dismissed because of the absence of palpable thyroid, eye signs, tremor, and nervousness in the sense of excitability. The only diagnosis that could be made, therefore, was auricular fibrillation of unknown etiology. This has been easily controlled by eleven cat units of digitalis per week.

Finally, about one year ago, it was decided to study the thyroid more thoroughly. The basal metabolic rate was found to be plus 28 per cent. Four subsequent determinations have all been above plus 20 per cent. These have led to a different view and the case is now looked upon as one of low grade hyperthyroidism which has produced auricular fibrillation.

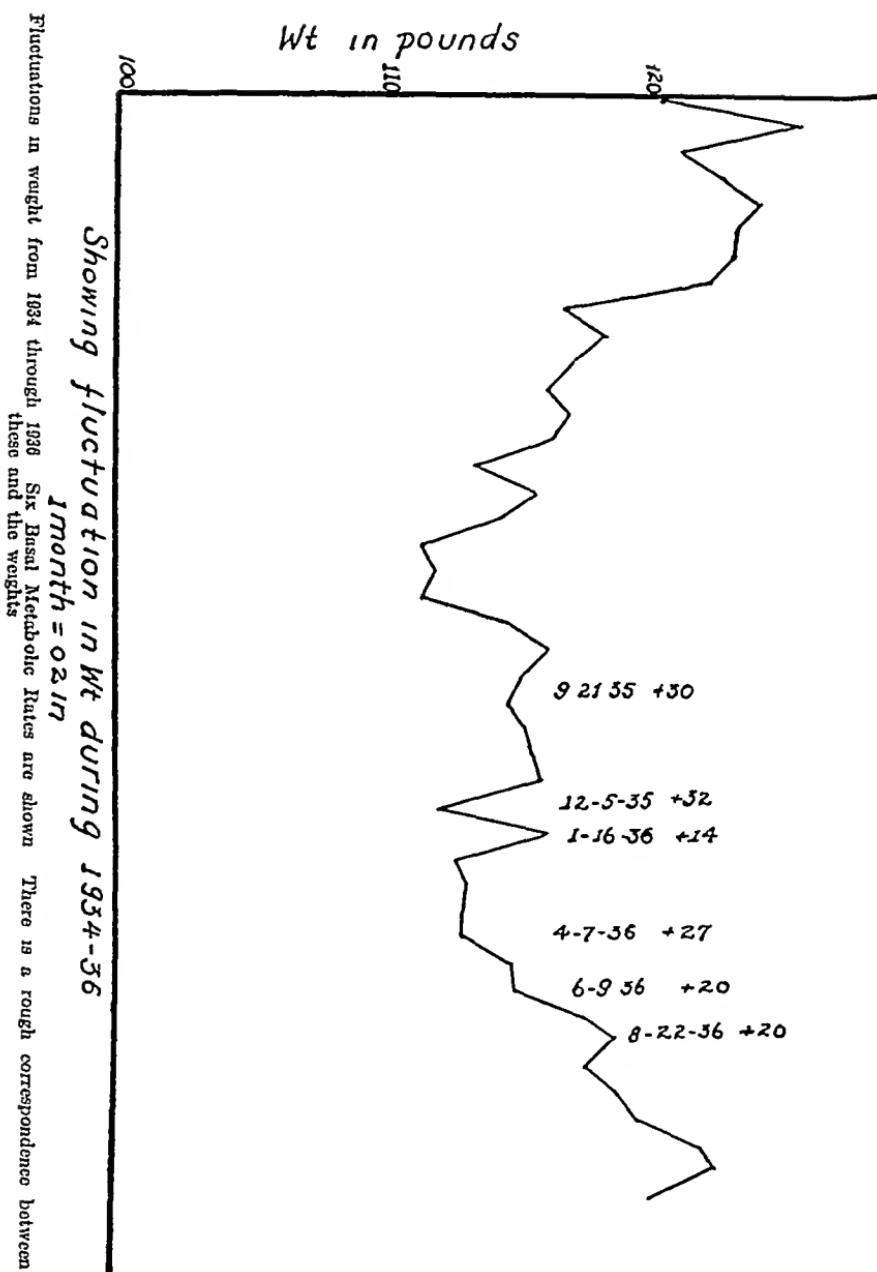
Comment — A low-grade hyperthyroidism which lasts for a long time is apparently unusual, for we have not found it frequently referred to. It resembles somewhat a form of the disease described by Morris,² in which the usual symptomatic manifestations of hyperthyroidism are present but the basal metabolic rate is normal. This

case we believe to be different, however, for the basal rate is constantly elevated though not greatly so.

This raises the question of what constitutes a normal rate. It has been pointed out that if one's basal rate is normally minus 10 per cent., a reading of plus 14 per cent represents a considerable increase. It is also to be remembered that heart failure per se produces some elevation of the metabolic rate.³ It is usually not as high as plus 30 per cent. This can hardly apply in this instance because congestive failure has never existed. Hyperthyroidism was very easy to overlook in this case for the reason that the usual clinical manifestations did not exist, probably because the metabolism has never been sufficiently elevated to produce them. There were at least two features that should have, and ultimately did, lead to a careful consideration of hyperthyroidism. These were, first, unexplained auricular fibrillation, originally paroxysmal and later permanent, and, second, fluctuations in weight. Auricular fibrillation either transient or fixed should always suggest the possibility of hyperthyroidism. In many instances, some other etiology will be discovered, but an over-active thyroid should always be considered if only to be ruled out.

Loss of weight is, of course, one of the cardinal symptoms of thyrotoxicosis. This patient had not lost weight in the sense of any striking change in his average weight. There were, however, constant striking fluctuations in weight with gains and losses of as much as 10 lbs in a month. Fluctuation in weight, as well as decrease in the average weight, we believe to be very suggestive of hyperthyroidism. So far as our incomplete studies permit, it appears that the weight is roughly proportional to the metabolic rate, for the weight was lowest with a reading of plus 32 per cent and greatest with a reading of plus 14 per cent (fig. I).

Apathetic Hyperthyroidism—We are accustomed to expect patients with hyperthyroidism to be very nervous in the sense that they are constantly active, alert, excitable, easily upset, and emotionally unstable. Lahey⁴ has pointed out that this picture need not be presented, but that individuals with marked hyperthyroidism and definitely high basal metabolic rates may, in contrast, be singularly apathetic. The second case illustrates this manifestation of hyperthyroidism.



CASE 2—P. H., white, aged forty eight, was well until three years ago when he weighed 200 lbs. He then began to become nervous and weak, lost considerable weight, and noticed that his heart beat rapidly and irregularly. After neglecting these symptoms for some time, he finally entered a hospital where hyperthyroidism was recognized and the administration of iodine was begun. He improved rapidly and gained 27 lbs in weight but refused operation and left the hospital. After three months, the original symptoms returned and progressed. Cardiac symptoms, consisting of breathlessness and a rapid irregular heart, were outstanding. During the past two years, he has been under the care of a number of physicians who fairly successfully controlled his heart failure but failed to stay the loss of weight. We judge that the role of hyperthyroidism in producing his heart failure was not appreciated.

The striking feature of the examination today is emaciation. The weight is now 100 lbs against 200 lbs three years ago. During all this loss of weight, the patient insists that his appetite has been excellent. We wish to emphasize the absence of the usual animation and activity seen in hyperthyroidism. In contrast, the patient is apathetic and almost lethargic. There is no tremor or nervousness. The heart is fibrillating, but this has been well controlled, and the ventricular rate was only 100 on admission a week ago, it is now 88. There is moderate cardiac enlargement, the total diameter being 140 cm., and there is a rather harsh systolic murmur at the apex. The blood pressure is systolic 110, diastolic 70. There is no striking congestive failure or breathlessness, which is attributable probably to the fact that the patient received digitalis for some time before his admission. The rest of the physical examination is negative. The past history together with the very elevated basal metabolic rate is sufficiently positive evidence to justify us in attributing the picture to hyperthyroidism, in spite of the fact that only the isthmus of the thyroid shows a slight nodular enlargement.

The first basal metabolic rate done six days ago was plus 89 per cent, a second determination made four days ago was plus 59 per cent. Lugol's solution (20 minims per day) has been started, but it is as yet too early to judge whether it is to be effective or not.

Comment—In this case, the weight loss has been so striking that a consideration of hyperthyroidism at the present time is unavoidable. However, one can readily see how the absence of nervousness, tremor, and eye signs might cause it to be overlooked if one saw this patient before the loss of weight became marked.

As in the first patient, the outstanding cardiac abnormality is auricular fibrillation. In the present case, however, one is not certain that there may not be organic heart disease as well as hyperthyroidism, for the apical systolic murmur is quite harsh and striking.

Hyperthyroidism in Old Individuals—The changes incident to old age may at times mask hyperthyroidism. Such findings as moderate loss of weight, tremor, and heart failure are not unexpected in old individuals and may easily be so explained, when in reality they

result from hyperthyroidism. We believe the next case illustrates this.

CASE 3—J. C., white, gives his age as sixty three but looks older. He entered the hospital ten days ago because of recurrent cough with expectoration, weakness, ankle edema, and breathlessness. These symptoms first appeared three years ago and have gradually progressed. During these three years he has lost 50 lbs in weight. At the time of his admission he presented the picture of severe congestive heart failure. Auricular fibrillation was present with a ventricular rate of 140, basal lung rales and breathlessness were marked, severe venous congestion was indicated by distended neck veins, hepatic enlargement, and edema. No important murmurs were present, and the heart was not found to be enlarged by clinical or roentgen ray examination. The blood pressure was systolic 110, diastolic 70. The thyroid was not palpably enlarged, and there were no eye signs suggestive of hyperthyroidism. Tremor of the hands and tongue was quite marked, but nervousness of the type we expect in hyperthyroidism was not striking. Clinical and roentgen ray studies of the lungs and gastro intestinal tract were negative. Although the picture did not at first suggest hyperthyroidism, the possibility of its existence was recognized and basal metabolic rates were determined. The first was plus 80 per cent, the second plus 77 per cent, and the third plus 70 per cent. These findings satisfactorily established the existence of hyperthyroidism.

Comment—Hyperthyroidism might have been easily overlooked in this case, the heart failure might have been readily attributed to arteriosclerotic changes alone. Similarly, the loss of weight and tremor might have been accounted for by the generalized arteriosclerotic changes, for neither is particularly unusual in senility. We, therefore, wish to emphasize that the picture presented by old, generally arteriosclerotic individuals, particularly when this includes heart failure with auricular fibrillation and emaciation, may at times obscure the recognition of hyperthyroidism. We are accustomed to think of thyrotoxicosis as a disease of young persons. Usually it is, but this case illustrates the fact that it may occur in old persons, we have been impressed recently with its frequency in persons over sixty and even over seventy years of age. When encountered in older age groups, the possibility of malignancy is to be thought of. This is unlikely in this case since the thyroid is not palpably enlarged in spite of the fact that the condition has apparently existed for three years.

DISCUSSION

We have presented these three cases of hyperthyroidism because we wanted to emphasize that the diagnosis of hyperthyroidism is not

always obvious or easy. Its recognition was made difficult either because the usual symptoms were not strikingly developed (Case 1), or because some expected signs such as nervousness and alertness and tremor were absent (Case 2), or for the reason that the signs or symptoms produced by hyperthyroidism could be attributed to some other cause such as senility (Case 3), or because a result of hyperthyroidism (heart failure) predominated and overshadowed the evidences of the fundamental condition (all three cases).

Although at times extremely difficult, the diagnosis will not be overlooked if one has in mind the possibility of thyrotoxicosis. In the three cases we have shown, the signs of hyperthyroidism are as inconspicuous and obscure as one is apt to see them. Yet, clues to its existence become obvious when one thinks of the possibility of hyperthyroidism and attempts to eliminate it.

Among some of the clues shown by these three cases which we wish to reemphasize and which should always suggest the possibility of hyperthyroidism are, loss of weight or instability of weight, transient or permanent auricular fibrillation, and heart failure without obvious or sufficiently clear cause.

In our opinion one of the most important contributions of modern cardiology is the emphasis which it has placed upon etiology. No cardiac disturbance can be considered to be properly diagnosed and completely understood until its cause has been determined. No matter, therefore, to what extent it may be masked—at least by heart failure—hyperthyroidism will not be overlooked if one approaches every abnormal cardiac manifestation from an etiologic point of view.

THE HEART IN HYPERTHYROIDISM

We cannot consider all features of this broad subject in the time available to us. We do, however, wish to discuss some of the phases that are suggested by the three patients we have shown and by one other case that we will presently discuss.

The Causes of the Cardiac Manifestations of Hyperthyroidism—Practically speaking, in every instance of hyperthyroidism, there is accompanying cardiac disturbance of some degree. This may be no more than a simple tachycardia, or it may reach the proportions of grave heart failure. In the past this cardiac derangement was attributed to a direct toxic action on the myocardium of the thyroidal

secretion, and almost every older classification includes hyperthyroidism as one of the causes of heart disease

In reading the older literature, it is a little difficult to be certain just how it was thought that hyperthyroidism produced heart disease. Most observers speak of myocardial damage and we have the impression that they were thinking in terms of specific structural change. However, as the importance of functional or reversible changes has become more and more appreciated and understood, there has developed an increasing tendency to discredit this view and to attribute the behavior of the heart to more tangible but indirect effects of thyrotoxicosis upon the circulation, such as the increased work that the heart must do, etc.

Among the reasons for this change of viewpoint are (1) Failure to demonstrate conclusively by experiment that thyroid secretion produces characteristic lesions in the heart even when histologic changes have been produced in animals, it has proven difficult to be sure that these were not the result of such mechanical factors as trauma, overwork, etc⁵ (2) The fact that although occasional evidences of severe myocardial degeneration have been found in human thyrotoxicosis, negative observations which failed to show any definite or specific change far exceed the occasional positive report⁶ (3) The frequent failure to find any clinical evidence of cardiac damage during active hyperthyroidism or after its abolition^{7, 8}

These considerations have led students of this subject rather generally to discard the view that a secretion of an hyperactive thyroid produces a specific histologic lesion in the myocardium, and to look more and more toward some of the established effects of hyperthyroidism on the metabolism for an explanation of the cardiac phenomena. Since these newer considerations of the cardiac features of hyperthyroidism are still unsettled, there are, as might be expected, a number of different views as to the manner in which cardiac reactions to hyperthyroidism are brought about.

Perhaps the plainest circulatory result of the elevated metabolism of hyperthyroidism is a great increase in the circulation rate, and a resulting marked increase in the work that the heart must do. In the eyes of some observers, all of the cardiac features of hyperthyroidism can be explained satisfactorily as mechanical or exhaustion effects that result from this increased effort^{5, 9}. Some feel that this may

produce sufficient trauma to bring about actual structural change in the myocardium⁵. Others, and these are perhaps in the majority, believe that the overwork of the heart incident to the increased metabolism is responsible, but that it does not directly produce change or disease. The hearts that fail, in their opinion, all have some pre-existing derangement secondary either to disease or to the degenerative changes of age^{10 11}, that hyperthyroidism acts as a catalytic agent¹¹ or "adjuvant" toward already existing but latent disease. To state this view in another fashion, hyperthyroidism does not produce heart disease,⁷ or still differently, a heart that is entirely normal can withstand the strain of hyperthyroidism, and will not fail.⁸

Another effect of hyperthyroidism that has recently received some emphasis is the fact that the muscle of the heart itself is involved in and affected by the greatly raised metabolism. This is suggested by such observations as the diminution or even exhaustion of the glycogen^{12 13} of the heart muscle and the increased lactic acid formation¹² that takes place in high grades of hyperthyroidism. To some observers, it seems probable that this altered cellular metabolism of the heart may play a dominant role in producing the cardiac responses seen in hyperthyroidism^{12, 13}. Still other students of this question feel that the heart is affected through a toxic action of a thyroidal secretion which does not cause permanent structural change but rather affects function only. According to this conception of the matter, the effects on the heart are reversible and are similar to those which produce auricular fibrillation in pneumonia¹⁴ or perhaps some of the changes that are produced by digitalis.

Somewhere among these various points of view probably lies the answer to the cause of the cardiac behavior in hyperthyroidism. Perhaps there is not one cause but a combination of causes. The matter cannot be settled now, and we prefer to leave you with an open mind toward it.

We now wish to discuss some of the features and problems of cardiac behavior in hyperthyroidism.

Auricular Fibrillation in Hyperthyroidism—This disturbance of rhythm, either as a transient or permanent affair, is frequently seen in hyperthyroid states. There is considerable discrepancy in the reported incidence of this disturbance. In some reported series it has been as high as 27 per cent,¹⁵ 6 per cent to 9 per cent is near

the average¹⁶ However, there is practically universal agreement concerning several features of this condition (1) The incidence is proportional to age, fibrillation being relatively infrequent in young, thyrotoxic individuals, and relatively common in older subjects, (2) the onset of fibrillation is not determined by the height of the metabolic rate¹⁴ nor by the duration of the thyrotoxicosis,⁹ (3) the presence of fibrillation is extremely important in determining whether congestive heart failure will or will not develop practically all observers agree that the great majority of hyperthyroid hearts that develop congestive failure do so only after the onset of auricular fibrillation, (4) auricular fibrillation in hyperthyroidism is often, perhaps usually, a reversible response, and frequently disappears spontaneously with the abolition of thyrotoxicosis

The cases we have so far shown you support these views to an extent, as does our general experience Its frequency and relation to age is shown by its presence in all three patients, the youngest of whom was forty-two years of age Two of the three cases had congestive heart failure In Case 1, auricular fibrillation developed and has been maintained, either as a transient or permanent disturbance, for a number of years in an individual who to judge by the history has never had severe hyperthyroidism

Various features of the behavior of auricular fibrillation have been used to support the several views on the cause of cardiac disturbances in hyperthyroidism Its infrequency in young persons has suggested that hyperthyroidism only seriously affects hearts already damaged either by age or disease^{7, 8} On the other hand, its occasional occurrence in young persons, in whom the degenerations of age or the presence of other types of disease are not likely, has been taken to indicate that hyperthyroidism produces a specific heart lesion¹⁷ The occasional onset of auricular fibrillation early in the course of hyperthyroidism before the metabolism has been greatly elevated and the work of the heart much increased has been interpreted to suggest that a toxic myocardial effect is important in deranging the heart¹⁴ The fact that fibrillation and failure may disappear with abolition of the hyperthyroidism and no trace of disease remain has been used to favor the view that overwork is the main responsible factor These several different interpretations that have been put upon auricular fibrillation show well the difficulties that

stand in the way of establishing a single cause for the behavior of the heart in hyperthyroidism

Cardiac Enlargement in Hyperthyroidism—The question of whether the heart enlarges in hyperthyroidism is an important one but not an easy one to settle, and different opinions regarding it have been expressed. Recently, Margolies, Rose and Wood¹⁸ analysed these opinions and found enlargement reported in from 25 per cent to 80 per cent of toxic thyroids when coexistent organic heart disease was rigidly excluded, the incidence fell to from 26 per cent to 32 per cent. Therefore, enlargement apparently occurs in approximately one-third of all toxic thyroids. Since these statistics have been derived mainly from living cases, the enlargement reported includes both dilatation and hypertrophy. It is fairly generally agreed that dilatation does sometimes occur with severe thyrotoxicosis to which the heart responds badly, being almost always seen in association with auricular fibrillation or flutter and congestive failure. The chief discrepancies in opinion concern hypertrophy. Recently Hurxthal¹⁹ has stated that if hypertrophy occurs in undiseased hyperthyroid hearts it is slight. On the other hand, Kepler and Barnes²⁰ in a recent study of eighty-nine necropsied cases which were free of hypertension and organic heart disease found hypertrophy in as much as 49 per cent of thyrotoxic subjects. This, therefore, like so many features of the thyrotoxic heart is unsettled and uncertain.

So far as it bears on the causes of thyrocardiac disease, the interesting fact is not so much that hypertrophy is present in more than one-third of all cases but rather that it is absent in more than half. Two of our cases are interesting in this connection. Cases 1 and 3 both had evidence of cardiac derangement in the form of auricular fibrillation in Case 3, this was accompanied by severe congestive failure. In both, hyperthyroidism had existed for a considerable period. Neither had demonstrable evidence of any cause for the cardiac derangement other than thyrotoxicosis, although both were in an age group where degenerative changes might be expected. Neither showed evidence of cardiac enlargement by clinical or roentgen ray study. It is certainly very unusual to find severe heart failure of the ordinary types develop and exist for three years in a patient of sixty (Case 3) who does not show obvious cardiac enlargement. Such instances in which fibrillation and congestive failure

occur without obvious hypertrophy have been construed as evidence against the hypothesis which attributes cardiac failure in hyperthyroidism entirely to overwork, since the principal effect of overwork as we know it in other forms of cardiac dysfunction is hypertrophy.¹⁴ However, to some observers this is not an entirely convincing objection since there is some evidence to indicate that the type of cardiac overwork in hyperthyroidism and hypertension, for example, is not the same, and may affect the heart differently. In hyperthyroidism the greatly increased circulation rate results in an increase in the work that the heart must do per minute but not per beat, whereas in hypertension, the circulation rate is not materially altered and the increased effort of the heart is directed toward overcoming peripheral resistance. It has been suggested that increased work per beat as well as per minute is necessary to produce cardiac hypertrophy.²¹⁻²²

Angina Pectoris in Hyperthyroidism—Attacks of precordial pain which have all the characteristics of angina pectoris are occasionally seen in older thyrocardiacs, they are rare in young subjects.²³⁻¹⁻²⁴ We wish now to present an instance of angina pectoris in a young woman with hyperthyroidism.

CASE 4—M. C., white, aged twenty five, is said to have had a goiter since the age of seven. When fourteen, metabolic rates varying from plus 25 per cent to plus 58 per cent were discovered and led to ligation of the superior thyroid artery. Following this, she did well until June, 1933. At the age of fifteen she married and has borne five children. During her last pregnancy she became slightly edematous and her blood pressure became elevated but subsided after delivery in May, 1933. Several weeks later symptoms of hyperthyroidism returned, the metabolic rates ranging from plus 30 per cent to plus 49 per cent. A subtotal thyroidectomy was performed in August, 1933. At this time her blood pressure was systolic 160, diastolic 95. The operation greatly improved her and she remained in good health until three months ago when there was a return of nervousness and palpitation, but no loss of weight.

Five weeks ago while walking on the street she was seized with a sudden, very severe precordial pain which radiated to the left arm. This forced her to stop, cling to her companion for support, and produced the sensation of impending death. Its duration was several minutes. Soreness remained in the left chest for four days afterward. During the five weeks she has been under observation, she has had two similar attacks which had all of the characteristics of angina pectoris.

The physical examination during the present admission has been largely negative except for slight tremor of the fingers and a moderately rapid pulse. There are no eye signs and no palpably enlarged thyroid. The metabolic rates have been plus 23 per cent, plus 21 per cent and plus 25 per cent. The examination of the heart is negative there is no enlargement, and there are no

murmurs. The electrocardiogram has been normal both during and between the anginal attacks. The blood pressure is now systolic 135, diastolic 88.

Comment—We have often wondered why the anginal syndrome is not more common in hyperthyroidism, for a consideration of certain established facts concerning the dynamics of the circulation in hyperthyroidism suggests that angina pectoris under certain circumstances should not be unexpected. The work of the heart at rest may be increased as much as 50 per cent in hyperthyroidism. During exercise or emotional stress, it is even more greatly increased. We cannot say that normal coronary arteries cannot meet the great demands thus created, but it seems plain that badly, or perhaps only slightly inefficient arteries may fail under the strain of thyrotoxicosis.²⁵ It has been pointed out that the lowering of the mean pressure which often occurs in hyperthyroidism may decrease the coronary blood flow and thus become another factor in precipitating anginal attacks.²⁶

Angina pectoris in young individuals with hyperthyroidism, who show no demonstrable evidence of cardiac disease, would constitute strong evidence that thyrotoxicosis damages the heart, for it is not probable that an undamaged heart would fail under the stress of hyperthyroidism to the extent of developing angina pectoris. The case we are discussing does not warrant this deduction, for, although there is no physical evidence of heart disease at present, there is a history of antecedent hypertension. For this reason it is safer to believe that this is an instance in which hyperthyroidism has precipitated angina pectoris in a heart which is perhaps slightly damaged.

SUMMARY

Four cases of hyperthyroidism have been presented and discussed. In three, the diagnosis was somewhat obscured because the manifestations of the disease were somewhat atypical, and because evidences of cardiac derangement of one form or another dominated the clinical picture. The fourth was a case of angina pectoris in a thyrotoxic woman of twenty-five years, who presented no definite evidence of organic heart disease. The atypical forms of hyperthyroidism shown by these three cases were (1) Low-grade but long-continued thyrotoxicosis, the only evidence of hyperthyroidism apart from unexplained auricular fibrillation was constant variation in weight (2) Apathetic

hyperthyroidism the usual nervous manifestations of the disease were conspicuously absent and were replaced by apathy (3) Hyperthyroidism in an old man in whom the thyrotoxic manifestations might easily have been attributed to the degenerative changes of senility

The present views regarding the causes of the cardiac manifestations of hyperthyroidism have been reviewed Auricular fibrillation, cardiac hypertrophy, and angina pectoris, particularly in their relation to the cause of thyrocardiac disease, have been discussed

We wish to express our appreciation to Dr T G Schnable and to Dr P A McCarthy of the Philadelphia General Hospital for allowing us to use Cases 2, 3, and 4 We are also very grateful to Dr D L Farley of the Pennsylvania Hospital for permitting us to use Case 1

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APPLIED THERAPEUTICS IN DISTURBANCES OF ENDOCRINE GLANDS WITH SPECIAL REFERENCE TO THE THYROID GLAND*

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THERE is no other field in medicine, to-day, that is attracting as much attention from physician, physiologist, pharmacologist, anatominist, biochemist, as that of endocrinology. To meet the universal enthusiasm with which endocrine gland products are prescribed, the clinician is bombarded with pamphlets extolling the virtues of various endocrine preparations, some offered as extracts of single glands, others as mixtures of many glands. In many instances, these preparations are inert and exert no more therapeutic effect than tap water, in other instances they may even be harmful to the patient. It behooves us, therefore, to adopt a critical attitude towards the use of endocrine gland products, for endocrinology offers abundant opportunity for making fanciful statements. To know what therapeutic agents to give a patient suspected of having some disorder of the endocrine glands, one must necessarily make the proper diagnosis and here the sound principles of general medicine must apply. No amount of laboratory data and hormone studies will replace clinical acumen and experience.

Let me illustrate this point by two recent experiences. Mrs M., aged thirty-four, began to complain of a lump in the neck which had been present about one and a half years. She had developed gradual weakness and tiredness in her legs, particularly after walking some distance. There had been a loss of forty pounds in weight during a year. About one year before, she had begun to see double for which an oculist prescribed glasses. Because of the weakness, the loss

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of weight, the presence of an adenoma of the thyroid gland and a basal metabolic rate of plus 17 per cent, a diagnosis of hyperthyroidism was made. Surgical intervention was contemplated. However on account of the presence of dysphagia, diplopia and ptosis of both eyelids, the diagnosis of myasthenia gravis was later substituted. The patient was placed on prostigmin and glycin. This treatment brought about great improvement in her condition and she was able to resume her household duties.

The history of the other patient illustrates quite well how much of a clinical waste basket endocrinology is fast becoming. This applies particularly to the too frequently made diagnosis of Cushing's syndrome. Mrs A K age, thirty-six years, (service of Dr Edward S Dillon), had been well until 1918, when she contracted influenza. Since then she had gained excessively in weight, hair had grown on the face and she had developed amenorrhea. For the two years prior to admission to the hospital, she suffered from attacks, two to three times a week, lasting three to five hours, during which a flush appeared upon the face, the eyes became red and she drooled saliva. When the attacks were on the patient did not move her limbs and would not talk. When the attacks subsided, she could move about somewhat and at times became delirious. Examination showed a middle aged, obese woman with most of the fat distributed over the trunk. The hands and feet were small. The chest was masculine in shape, the breasts were flat and atrophic. There was a heavy growth of hair on the chin and upper lip. Pubic hair was feminine in distribution. The examination of the lungs and heart revealed no gross abnormality. The blood pressure was systolic 160, diastolic 110. The examination of the abdomen revealed nothing abnormal. The examination of the skull was negative. The visual fields and ocular fundi were normal. The basal metabolic rate was plus 2 per cent. The sugar tolerance test gave the curve characteristic of diabetes mellitus. The diagnosis of Cushing's syndrome or a tumor of the adrenal cortex was made. Retrograde pyelograms of the left kidney showed dilatation and elongation of the pelvis and major calyces and the presence of an adrenal tumor was suggested by the roentgenologist. The patient was submitted to an exploratory operation. No tumor of the adrenal was found. The left adrenal was removed together with a portion of the tail of the pancreas which has been mobilized during

the operation. After operation the patient went into shock and in spite of treatment failed to rally. She died thirty-six hours after the operation. The autopsy showed no abdominal abnormalities. The microscopic examination of the brain showed degeneration of the tuber-cinereum and of the cerebellum probably due to encephalitis.

In applying therapeutic measures in endocrine gland disturbances, one should bear in mind that endocrine upheavals are usually of the hyperfunctioning or hypofunctioning types. Therefore, the therapeutic program consists either of replacement therapy or the use of means medicinal, surgical or radiological to depress the functioning of the overacting gland. Another factor to bear in mind is that in endocrine gland disturbances, just as in other medical conditions, the dosage of a certain endocrine compound varies in individual cases.¹ In endocrinology this is particularly to be stressed, because the inherent capacity of tissues to respond to endocrine stimulation varies in different persons. Take for instance thyroxin. Equal amounts of this compound will produce different effects in different individuals, not only in so far as the cardiac, nervous or other bodily tissues are concerned but also as regards the effect upon the basal rate.² The interrelationship between glands of internal secretions is so striking that frequently the function of an endocrine organ is influenced by the abnormal functioning of other endocrine organs. This intimate functional interrelationship between various ductless glands occurs through the intermediary of the autonomic nervous system. Consider the well known clinical facts of the interaction between the thyroid, the adrenals and the autonomic nervous system. The clinical picture of Graves' disease is made up largely of symptoms due to disturbance of the sympathetic nervous system conditioned by excessive adrenal secretion. However, the therapeutic approach is primarily through the thyroid. A combined disturbance of several endocrine glands in one person, or as it is called the pluriglandular syndrome, requiring the administration of pluriglandular products, is, in my experience, rarely met with. It is usually one gland which is primarily disturbed, although other glands may secondarily partake in the disorder. Other facts that should be borne in mind are that a ductless gland is not stimulated by its own secretion, and that the prolonged use of glandular products may not only produce a refractory state, supposedly because of anti-hormone formation, but may actually inhibit secretion.

FIG. 1

A

B



A Hyperthyroidism in child eleven and a half years of age. Enlargement of neck, nervousness, irritability, loss of weight, tachycardia of two years duration. Basal metabolic rate plus 63 per cent. Rest in bed compound solution of iodine and subtotal thyroidectomy.

B Same patient three weeks after operation
Pathological diagnosis Diffuse toxic goiter

Fig. 3



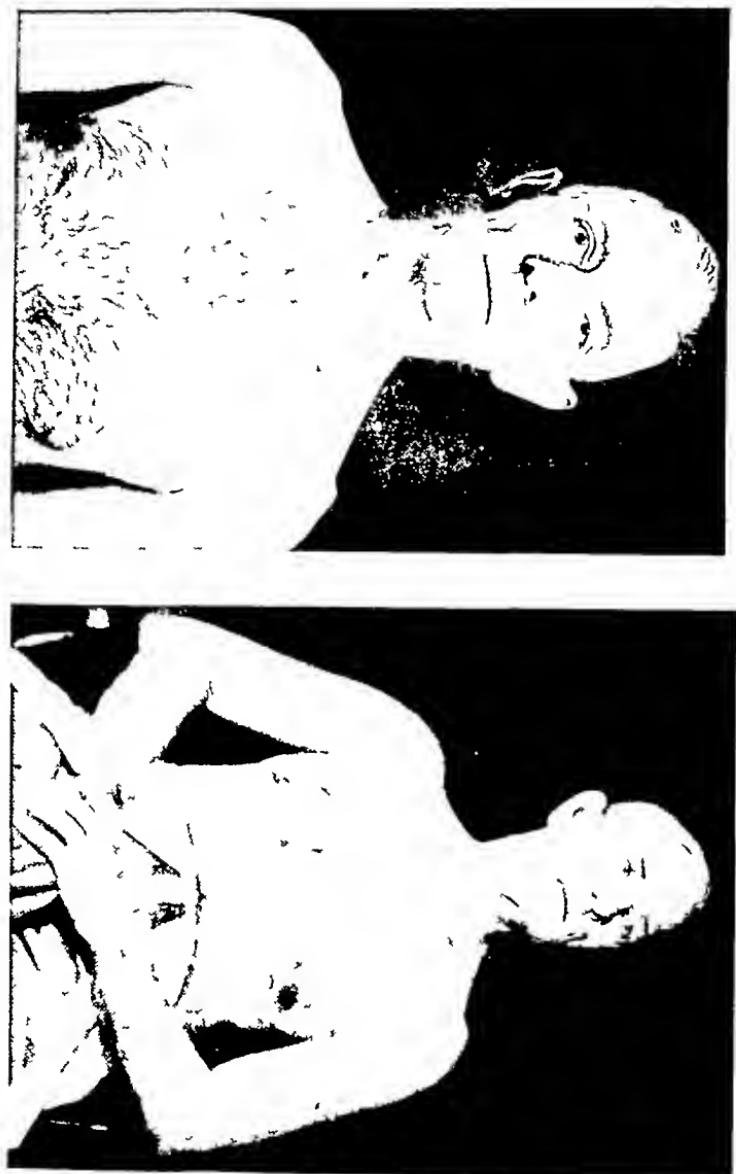
Diffuse toxic goitre in child eight years of age. Nervousness, anxiety, nervous irritability, loss of weight and attacks of diarrhoea. Symptoms of four years duration. Pulse 120. Blood pressure systolic 134 diastolic 80. Proptophobia. Diffuse symmetrical diffuse enlargement of the thyroid. Basal metabolic rate plus 41 per cent. Compound solution of iodine and a course of irradiation brought about gain in weight (10 lbs) and marked general improvement. (Courtesy of Dr. Wm. N. Bridgman.)



Fig. 2

Toxic nodular goitre. This patient aged fifty years was treated in a cardiac clinic. He developed nausea which was thought to be the to the thyroid. The medication was stopped for two weeks but nausea and weakness continued. Pulse 70. Blood pressure systolic 112 diastolic 90. Skin of body warm but dry. Thyroid palpable. Basal metabolic rate 53 per cent plus. Compound solution of iodine taken for two weeks reduced the basal metabolic rate to 23 per cent plus. Subtotal thyroidectomy brought about marked improvement. Basal metabolic rate on discharge from the hospital 5 per cent minus. Pathological examination of the thyroid. Grossly toxic nodular. Microscopic diagnosis is toxic nodular. Courtesy Dr. Wm. L. Reiter. (Courtesy Dr. Wm. L. Reiter.)

FIG 4

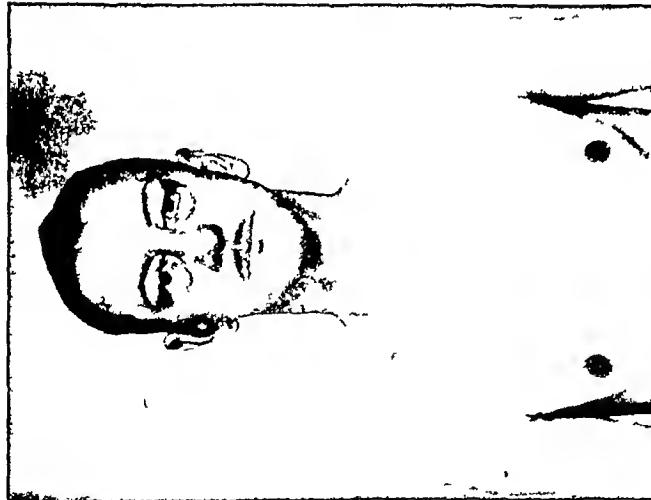


A

B

Hyperthyroidism in man aged fifty-six years. Loss of weight
were the outstanding clinical manifestations. Basal metabolic rate 46 per cent plus
course of Irradiation brought about a cure (Courtesy of Dr L B Horwitz)

FIG 5



Hyperthyroidism with marked edema of both lower ^{the lids}. Patient age thirty-eight years presented typical symptoms of hyperthyroidism. Basal metabolic rate 61 per cent plus. After three weeks of bed rest high endocrine diet and compound solution of iodine the basal metabolic rate declined to 20 per cent plus. Repeated surgery or irradiation. One year later patient was seen again in a thyrotoxic state.

FIG 6



Hyperthyroidism masked by symptoms of night terrors in patient age forty-one years. Substernal oppression, shortness of breath and pain, radiating to left shoulder and arm. Attacks relieved by nitroglycerin. Subject to 3-4 attacks daily. Blood pressure diastolic 56 systolic 120. Electrocardiogram sinus tachycardia and left ventricular preponderance. Thyroid not palpable. Eyes widening of the palpebral fissure. Basal metabolic rate plus 70 per cent. Compound solution of iodine abolished anginal attacks. Basal metabolic rate reduced to plus 34 per cent. Surgery rejected. Three and half months later patient reentered hospital with agonizing anal pains which continued for three days. She died before thyroectomy could be undertaken.

of other glands. Thus, for instance, there is enough experimental evidence to show that prolonged administration of female sex hormone will inhibit the gonad stimulating function of the anterior pituitary lobe.³ Relatively large doses suppress the diabetogenic function of the anterior pituitary.⁴ The inhibition of the diabetogenic factor of the hypophysis through theelin injections is said to alleviate diabetes mellitus. For the present at least, this procedure in the clinic seems unwarranted and should await further trials.

This preface leads to a clinical appraisal of the value of endocrine gland products in disorders of the endocrine glands. I shall begin with disturbances of the thyroid gland. From a therapeutic point of view it is convenient to group them into the hyperfunctioning and hypofunctioning types. The hyperfunctioning type may manifest itself clinically as toxic diffuse goitre, toxic nodular goitre and monosymptomatic type.⁵ In hyperthyroidism, the plan of attack consists in measures to reduce the hyperactivity of the thyroid gland. The three measures most commonly employed are

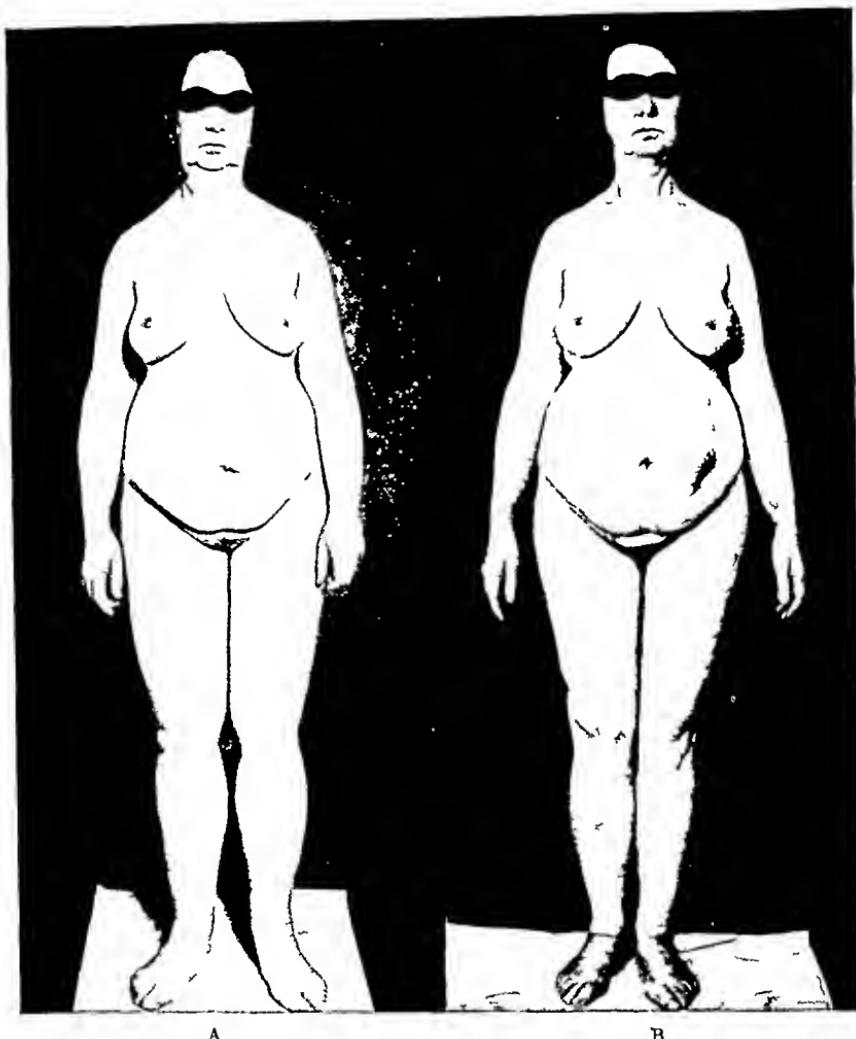
- 1 Iodine administration
- 2 Irradiation
- 3 Surgery

Iodine metabolism is closely related to the thyroid gland paralleling the relation of carbohydrate metabolism to the pancreas or of calcium metabolism to the parathyroid glands. The thyroid gland when secreting normally contains about 20 mg of iodine per gram of dried gland. Thyroxin, the crystalline active principle of the thyroid, is high in iodine content, consisting of 65 per cent iodine. Iodine is essential in the treatment of hyperthyroidism. The action of iodine in hyperthyroidism can best be illustrated by a contrast of the histology of the normal gland with that of the gland after iodine therapy. The normal secreting unit of the thyroid gland is the follicle. It is a rounded, grape like, closed vesicle, lined with flat, cuboidal, epithelial cells. Within the lumen of the vesicle, there is a moderate amount of well stained colloid material. In hyperthyroidism, the epithelial cells become high columnar in character and form many papillary like projections into the lumen of the acinus. The stainable colloid within the lumen is greatly decreased in amount.

The iodine content of the gland is lowered to as low a figure as 0.4 milligram per gram of dried gland. The iodine in the blood, at this time, rises in amount from a normal of 11 gamma per 100 cc blood to a value of 15 to 39 gamma per 100 cc blood.⁶ Curtis⁷ found an increased blood value in hyperthyroidism to average twenty-seven micrograms per cent. The urinary iodine excretion is increased to several times its normal. The average normal urine iodine elimination is between thirty-six to seventy-eight micrograms per twenty-four hours.⁸ When the hyperthyroid patient is placed on iodine, certain involutional changes occur in the thyroid gland. There is a shrinkage of the high columnar cells and they appear first cuboidal, then flat cuboidal, and within the acinus there is an increased accumulation of heavily staining colloid material. The number and the size of the papillary infoldings decrease, the iodine content of the gland rises sharply and may be as high as eight milligrams of iodine per gram of dried gland.⁹ The iodine rise somewhat parallels the increase in stainable colloid. The vascularity of the gland diminishes. The gland becomes firm and as a result of the increased size of the follicles, the vascular and lymph channels become for a time obstructed.¹⁰ Because of the obstruction, due to pressure from the accumulated colloid, less thyroxin enters the blood stream, and the manifestations of the disease are greatly lessened in intensity. The blood iodine level as well as the basal metabolic rate decrease. The basal metabolic rate is lowered 2 to 4 points daily on iodine administration. In our experience, however, there is no correlation between the clinical severity of the disease, the basal metabolic rate and the concentration of the blood iodine. The pulse rate, dyspnea and palpitation decrease and there is noted a most pronounced effect on the nervous and gastrointestinal symptoms. The patient generally gains weight, enjoys a feeling of comparative well being both mentally and physically. His nervous tension relaxes.

This iodine remission occurs in the majority of cases in from seven to fourteen days. It is this involutional stage, which is generally agreed upon to be the ideal time for surgical intervention. If the patient is not operated upon at this favorable time, the symptoms of hyperthyroidism usually return. There results an increase in the basal metabolic rate, the tachycardia, the loss of weight and the nervous instability. The administration of iodine may become less

FIG. 7



A

B

Myxedema in woman aged fifty-four
A Note bloated puffy face dull expression coarse hair Obesity Swelling of both ankles legs and wrists Basal metabolic rate 42 per cent minus Blood cholesterol 400 mg per cent per 100 cc blood Patient's complaints were hoarseness deafness, inability to concentrate

B Same patient after five months treatment with desiccated thyroid

FIG 8



Hypothyroidism Bizarre nervous complaints loss of weight nausea vomiting and asthenia Basal metabolic rate minus 30 per cent Blood cholesterol 242 mg per 100 cc blood (Service of Dr Wm L Robertson)

Fig. 9



Childhood myxedema. Patient who
twelve years had been taking thyroid
preparations since the age of two years.
Height 57½ inches weight 122 lbs. Men-
struation regular since thirteen years of age.
Intelligence quotient 63 (Stanford revision of
Binet test). Has no industrial competence
but is able to assist with general housework.

effective and one may have difficulty in bringing about another iodine remission. The patient is said to have become "iodine fast." The surgical risk at this period is great. To overcome the patient's refractoriness to iodine one should completely withdraw iodine administration for a period of from two to four weeks and then place him again on iodine. It is to be emphasized that according to the experience of most clinicians, iodine does not produce any permanently beneficial effects on the course of the disease. The cause of this probably lies in the fact that the temporarily decreased vascularity which occurs during involution is no longer in evidence since the blood vessels and lymph channels adapt themselves to the new conditions and thyroxin enters the blood stream in increased amounts.¹¹

Nodular toxic goitre is effected in a similar manner by iodine and exhibits the same cycle of cell changes but more irregularly and to a lesser degree. It should be used preoperatively in the same manner as in diffuse toxic goitre.¹² The fear that the nodular toxic goitre may be made worse by iodine is not confirmed by clinical experience. One is, therefore, forced to conclude that both in diffuse and nodular toxic goitres, operation offers the best therapeutic approach after the proper preparation and in the great majority of patients will result in marked clinical improvement or cure.

Iodine should be used postoperatively to prevent excessive regeneration of the remaining thyroid gland. The dosage of compound solution of iodine is usually ten minimis three times a day for a period of ten to twelve days before the operation. One may prescribe five to ten minimis of a saturated solution of potassium or sodium iodide once daily.¹² After the operation, the patient is placed on ten minimis of compound solution of iodine three times a day for one month and then again on ten minimis once daily during the second month. After the regenerative period the patient should be advised to use iodized salts or to take a ten milligram iodine tablet weekly. The clinical value of iodine in preventing recurrence has been questioned recently.¹³ It should be remembered that in goiterous regions larger amounts of iodine are required than in nongoiterous areas. It is well known that the severity of the disease is greater in the goiterous regions than in the non-goiterous regions. However, large amounts of iodine are not necessary. An excessive dose does not necessarily give the desired optimum response. There appears to be a definite threshold beyond

which the body will not take up at one time any further amounts of iodine. It will be excreted by the kidneys and will have no beneficial effects. Iodine then is used preoperatively to prepare the patient for a thyroidectomy, postoperatively to prevent regeneration and recurrence of the disease. In addition to iodine, rest, sedatives, such as bromides or phenobarbital, a high carbohydrate diet to store glycogen in the liver, and increased fluid intake are of great benefit as preoperative measures. In certain mild cases iodine may be used as an expedient. These are the cases in which the fire smolders for years, in such cases iodine may relieve symptoms. It is best in these chronic cases to discontinue iodine from seven to ten days each month.

It is to be regretted that excepting a small series of cases reported by Kassel, Lieb and Hyman¹⁴ and those of Thompson et al²⁴ (whose patients received syrup ferrous iodide) no other study is known of consecutive cases of hyperthyroidism treated with iodine alone. As Beckman¹⁵ states "what the surgeons are prone to forget is that not all physicians are using iodine unskillfully. How are they using it and with what results, that I do not know, but some day the answer will be forthcoming."

The value of irradiation in hyperthyroidism is controversial at the present time. In some patients it seems to be effective but is inferior to operation.

Thyroid hypofunction is observed in

- 1 Simple goitre
- 2 Myxedema
 - a Infantile cretinism
 - b Adult Gull's disease

Marine and Kimball have shown in their work at Akron, Ohio, that simple adolescent goitre is easily preventable by the use of iodine.¹⁶ Simple goitre develops most often before sexual maturity, especially in girls. It also appears not infrequently during pregnancy and lactation, and during the decline of sexual life. The symptoms are few and are not serious except when the goitre is large enough to cause displacement of the larynx and trachea and interfere with respiration. Goitre is generally held to be due to a deficiency of iodine. That withdrawal of iodine from human diets is responsible for development of goitre, is evident from the experience with Indian tribes

Indian tribes which are free from goitre when living on a salmon diet which is rich in iodine, develop goitres when salmon is excluded from their diet. The normal need for iodine varies with different age groups, physiologic cycles of life and geographic locations. However, an adult requires from 0.04 to 0.08 mg per day. Thompson¹⁷ calculated that the iodine requirement of the normal thyroid is about 0.2 mg a day. For the prevention of goitre one may use iodized table salt furnishing approximately 1.0 mg of iodine each day, or administer a chocolate coated tablet containing 1/6 of a grain of organic iodine once a week throughout the school year and during pregnancy. The following preparations are used: iodocasein, iodo-starin, oridon. For treatment of simple goitre small doses of iodine may in some cases decrease the size of the goitre, although in the majority of instances it is not curative. The reason that iodine is so ineffective is due to the deficiency of the cells lining the acinus and to their inability to manufacture sufficient thyroxin. The administration of small doses of desiccated thyroid, e.g., one grain three times daily, will put these cells at rest until the colloid can be absorbed and the cells come back to normal.¹⁸

According to Mordl,¹⁹ cretinism originates during fetal life or in infancy. It is due to total failure of thyroid function. It frequently results from hypothyroidism in the pregnant mother or because of insufficient iodine in food of the pregnant mother. The intimate interrelationship between the thyrotropic hormone of the anterior pituitary and the thyroid gland must be borne in mind in considering the pathogenesis of cretinism. In the light of this interrelationship there is a possibility of a primary insufficiency of the anterior pituitary as a contributory factor in the origin of cretinism. When treated very long and persistently with thyroid extract, cretinism may improve. Childhood myxedema gives a better response to thyroid extract.

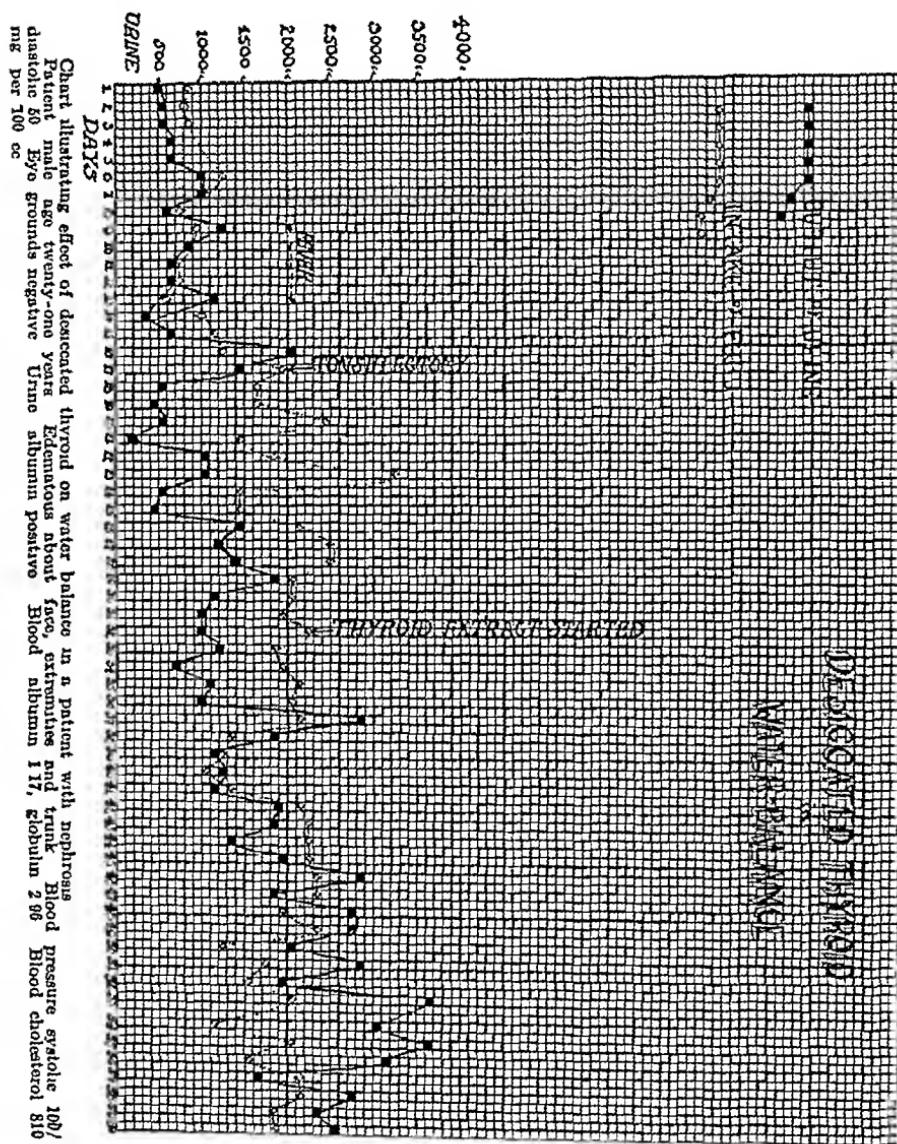
Patients with fully developed myxedema (Gull's disease) are comparatively rare. It is occasionally seen in women at the menopause whose hypothyroid syndrome may be masked by the vasomotor symptoms of the menopause. The full blown picture of myxedema develops usually when the basal metabolism level has persisted below minus 30 per cent for weeks and months.²⁰ Postoperative myxedema is not an uncommon occurrence among patients in thyroid clinics.

Three such patients were studied in the Endocrine Clinic of Temple University Hospital in the past two years whose outstanding manifestations were weariness, tiredness and severe anæmia. Two of them responded to oral administration of iron and desiccated thyroid, and in the third patient, intramuscular liver injections had to be resorted to in addition to the iron and desiccated thyroid therapy.

Hypothyroidism without myxedema is of frequent occurrence. These patients present a paucity of physical signs. They may be underweight rather than overweight. Their complaints are varied and bizarre. Tiredness and lack of endurance are prominent features in their histories. Most of them complain of being nervous and irritable and they suffer from attacks of depression. Neuroasthenia or hyperthyroidism is frequently suggested. The internist is often surprised when it turns out that they have a high blood cholesterol and low basal metabolic rate. It is noteworthy that the complaints of these patients have no special reference to any particular organ. Constipation with hypoperistalsis is commonly present in this group of patients.²¹ Lisser²² has recently given a good description of "The capricious vagaries and hidden hints of thyroid failure."

There are two different strengths of thyroid substance exclusive of the crystalline hormone thyroxin. Thyroid U S P (desiccated thyroid) is standardized to contain 0.17 to 0.23 per cent iodine. Another method of designating strength of thyroid preparations has grown out of the practice of some pharmaceutical houses to label their product in terms of fresh rather than desiccated gland substance. It should be remembered that one grain of desiccated thyroid gland substance is roughly equivalent to five grains of fresh gland. These variations in strength of preparations should be kept in mind when prescribing thyroid medication. It is safe to begin with one half grain desiccated thyroid extract once or twice daily. If no untoward symptoms develop within ten days, such as nervousness, excitability, excessive perspiration, palpitation, loss of weight, the dosage may be increased until a "maintenance dose" is reached. The average maintenance dose in a patient with myxedema is about three grains daily. In some patients the dose required may be considerably larger and may be continued for weeks without the production of untoward symptoms. On the other hand, it should be borne in mind that large doses may induce acute symptoms of thyrotoxicosis in a comparative short

period of time. In one of our patients with colloid goitre and a basal metabolic rate of minus 6 per cent, the administration of two grains of desiccated thyroid three times daily for a period of three weeks has



brought about an acute attack of thyrotoxicosis²³. The best method of treatment, therefore, is to administer small doses and gradually increase until the minimum amount is given that will maintain the pa-

tient at a normal metabolic level. In the milder form of hypothyroidism, the patient's gland may resume, more or less, its function and the maintenance dose may be decreased or omitted altogether. However, such instances are rare. In the majority of patients, the administration of thyroid will have to be continued for many years similar to insulin administration in diabetes mellitus.

Thyroid extract has also been found useful in some non-thyroid conditions on account of its diuretic effect. In a patient with nephrosis at the Philadelphia General Hospital, service of Dr. Schaefer, with a blood cholesterol of 810, improvement was brought about when desiccated thyroid was administered, after all other measures failed. Thyroid extract may also be given to stimulate other endocrine glands such as female gonads and the pituitary. In obesity, desiccated thyroid is still a useful drug when given under a physician's supervision.

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Diseases of Metabolism

DIABETICS—WHAT OF THE FUTURE?¹

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WHAT of your future as an individual diabetic, what of the future for all diabetics, what direction will further investigations take, what improvements may we expect in the treatment of diabetes?

When I ask these questions I cannot help but think back to thirty years ago when I was seeing my first cases of diabetes, and to the answers I had to give mothers of diabetic children and to diabetic patients to questions exactly like these. I remember particularly how painful then were my experiences with children, how pitiful these little ones were, and how much courage one had to inspire in the hearts of their mothers who saw them actually fading away under their eyes. Even then it was my custom to say, "Hold fast, obey the rules even though they seem to torture the little one by unnecessary deprivation in view of the utter lack of promise of cure or indeed of prolongation of life. Hold fast because some day will come a material, probably from the pancreas, which will furnish what the little patient lacks, and will serve to keep and maintain him. I do not know when that will come, but if your child is here then he will benefit by it. If it comes soon after his death you may reproach yourself for not having, in spite of your trials, struggled to prolong his life." How happy we are to-day to contrast this picture with the happy, joyous, apparently healthy, diabetic children who are growing up around us since the inauguration of the insulin era. Diabetic coma in those pre-insulin days, too, was uniformly fatal and was responsible for a large proportion of deaths in diabetics. To-day, the deaths from diabetic coma have dwindled because diabetic coma is not so frequent, and because in a number of series of diabetic comas the

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mortality rate has ranged from five to ten per cent, instead of the former hundred per cent. I remember, too, the dietetic difficulties not only of those days of thirty years ago, but of the nearer times of the Allen under-nutrition treatment, and I contrast those diets with the generous and appetizing diets of these high carbohydrate feeding days. I recall, too, that formerly the diabetic was a "noli me tangere" for the surgeon, whereas to-day the diabetic may safely share in all the benefits of modern surgery. Nor must I forget to enumerate among the blessings that have come to the diabetic within the span of my professional life the new gift of protamine which has reduced the number of injections, and which promises even greater freedom of life than has previously been the lot of the diabetic.

I am still in the habit of saying to my patients, "Hold fast, obey the rules, make sure by obeying them that you will so prolong your life and health that you will be here as long as possible to share the blessings that are still to come." Just as I was sure that some day insulin would come, so am I now sure that we have not yet reached the limit of what can be done to help the diabetic, nay even to prevent his diabetes, or even to cure it when once established. It is the theme of this paper to develop the basis for this belief. The last twenty years have produced so much in the way of a better understanding of the physiology of the metabolic processes disturbed in this disease that we cannot hope for much more development of our knowledge in this direction. Yet there are still some phases of the inter-relations of the endocrine glands which remain to be explored. It may well be that some of the new light that is to come in the future will shine from this direction. The occurrence of glycosuria in hyperthyroidism has been well known for a long time. The distinction between the glycosuria of hyperthyroidism and true diabetes has not been so long known, and as a matter of fact is not clearly made to-day. Joslin, for example, distinguishes between the glycosuria of hyperthyroidism and true diabetes on a purely arbitrary basis. "It is our rule to regard a blood sugar of 0.17 per cent following a meal as indicative of diabetes. When diabetes and hyperthyroidism co-exist, then it is helpful to raise the post prandial value for venous blood from 0.17 to 0.20 per cent, thus excluding a large number of individuals who otherwise would seem to have been cured of their diabetes following a successful thyroid operation."¹ Still less understood

is the occurrence of undoubtedly a true diabetes concomitantly with hyperthyroidism, and the undoubted reduction in the insulin requirement in such a patient following subtotal thyroidectomy. It is, of course, believed that this reduction in the insulin requirement is largely due to the slowing of the metabolism, and indeed thyroidectomy has been proposed and carried out as a mode of treatment of diabetes mellitus without hyperthyroidism.^{2,3} It is by no means certain, however, that the role of the hyperactive thyroid in diabetes is merely that of instigator of increased metabolism. Further investigation may teach us even more than we now know of the antagonistic action of thyroxin and insulin. Similarly we may look forward to the extension of our knowledge concerning the relation of the hypophysis to the pancreas, or at least the hypophyseal secretion to insulin. I have time to allude only cursorily to the contributions of Houssay,⁴ Barnes and Regan,⁵ and Long and Lukens.⁶ Houssay and Biasotti showed that pancreatectomy produces an intense diabetes in toads. If the pituitary, or only its glandular lobe, were removed, pancreatectomy did not provoke glycosuria and the blood sugar increased slightly or not at all. If then the anterior lobe of the hypophysis were implanted beneath the skin an intense diabetes was observed. The frequent occurrence of glycosuria in patients with acromegaly (in which disease there is usually an adenoma of the pituitary) was early remarked upon by Pierre Marie and others, and has been commented upon by numerous authors since. There have been, however, laboratory demonstrations showing the effect of injections of extracts of the anterior pituitary lobe producing hyperglycemia and glycosuria. Houssay and his co-workers⁷ have found such an action even in animals previously deprived of the thyroid and hypophysis. I must refer briefly to the effect of epinephrin injections in producing hyperglycemia, and to the increase in sensitivity to insulin caused by the removal of the adrenal glands. The inter-relations of these various endocrine glands still remain a mystery, and in that mystery possibly lies the explanation of the disease which we call diabetes.

The chain of circumstantial evidence incriminating the pancreas, and specifically the islands of Langerhans, would seem to have been closed by the demonstration of the control of experimental diabetes by insulin. First the demonstration by Minkowski and von Mering that pancreatectomy makes experimental animals diabetic, next the dem-

onstration by Opie and others of the hydropic degeneration of the islet cells, then successively the failure after many attempts to produce a pancreatic extract capable of controlling diabetes, the suspicion that this failure was due to the digestive action of the pancreatic enzymes upon the internal secretion, the demonstration by Allen and others that ligation of the pancreatic duct causes atrophy of the acinar tissue leaving the remnant composed entirely of islet tissue, the animal remaining non-diabetic until this remnant was subsequently removed, the preparation of insulin by Banting and Best from such a pancreatic remnant. The conclusion would seem to be inescapable that the site of the disease in diabetes is in the islands of Langerhans. When we turn, however, to find the *corpus delicti*, as the lawyers would put it, and produce evidence of the damage or destruction of this islet tissue, we fail utterly.⁸ Particularly impressive is the report of Shields Warren who in a series of three hundred autopsies on diabetic patients found no changes in the pancreas that were not also found in normal people, but he found these changes more frequently in diabetics. In twenty-five per cent of the autopsies on diabetics he found no changes in the pancreas at all.⁹ Joslin¹⁰ has reviewed the evidence of regeneration of the islet tissue, occurring not only in the pancreatic remnants of partially depancreatized dogs but also in the pancreas of non-diabetic patients dying of other causes, and in the pancreas of diabetic patients dying of various causes. Similarly, hyperplasia of the islet tissue has been found in the fetuses of diabetic mothers. In the light of such evidence of regeneration and of hyperplasia the thought arises of the possible chance of developing treatment directed to the production of such a hyperplasia, if further investigation may convince us that such a procedure would be of benefit to the diabetic. In this connection one remembers cases of spontaneous hypoglycemia of extreme grade which have been reported as apparently due to carcinoma of the pancreas.¹¹ If the hyperinsulinism in these patients is due to the increase in the number and function of the islet cells because of the neoplasm we may ask ourselves, as I have indicated, whether we may not produce an increased insulin function by a method still undetermined. Before I leave this subject of the pathology of the pancreas I wish to quote with emphasis what Joslin has written, "Indeed, one is tempted to wonder whether

the changes in the islands may not be the result rather than the cause of diabetes".¹²

Consideration of the field of etiology brings no further clue as to the probable nature of the disease. It cannot be doubted that adiposity is associated with diabetes,—more than half of the diabetics are, or have been, fat, but to say that the two, diabetes and adiposity, are associated is not the same as attributing one to the other. It may well be that the metabolic fault which produces diabetes is the same fault that produces adiposity, or it may be that faulty habits of living (under-exercising and over-eating) favor or precipitate the metabolic dysfunction which we know as diabetes as well as produce adiposity. The role of heredity in the production of diabetes is a strong one. Diabetes seems to be a recessive characteristic in the Mendelian sense. To recognize this does not necessarily imply the acceptance of some fundamental structural somatic abnormality passed on from generation to generation. When I consider these two factors, adiposity and inheritance, together I am not altogether convinced of Joslin's dictum that "Jews are diabetic not because they are Jews but because they are fat Jews." I have seen too many thin diabetic Jews to be able to subscribe to this. In searching for an explanation for the frequency of diabetes among Jews I have had my attention arrested by two facts. The first of these concerns the inbreeding of the Jews. I believe it is not well known that throughout the Middle Ages and up to half a dozen generations ago marriages between first cousins was not only permitted but encouraged among the Jews. In addition to this custom which has ceased to operate extensively in the last hundred years, we must remember that Jews have been mating with Jews and that the opportunity to breed out diabetes has been less in their case than in the case of other races less diabetic. The other fact which I have had in mind is the well-known nervous instability of the Jew. There is an unusual lability of his nervous system which some of us might be inclined to attribute to the abnormal conditions of persecution and daily and hourly uncertainty under which the Jew has lived in Europe throughout many generations. I must confess, however, that this argument, namely that the lability of the nervous system may have something to do with the precipitation of diabetes, has lost a good deal of its force by the experience of the World War. Certainly the strain of the war should have caused an

increase of diabetes had this been the case, and I am compelled to record the statement of Von Noorden quoted by Joslin¹³ "neu-rogenen Diabetes gibt es überhaupt nicht, die Kriegserfahrungen haben ihn vollends zu Grabe getragen" (Neuogenous diabetes does not exist, the experiences of the World War have completely destroyed this conception) There remains, however, it seems to me the possible conception of the Jews being predisposed to diabetes just as we have learned that certain anthropological types are predisposed to cardiovascular disease and to tuberculous disease Equally futile is the consideration of the possible role of infections in diabetes I think it may be fairly stated that the overwhelming clinical evidence is against the significance of syphilis in diabetes The diabetic may become syphilitic, and the syphilitic may become diabetic but the two stand in no causative relationship Acute infections do seem sometimes to precede the sudden appearance of diabetes in children, but this does not necessarily mean that the acute infection has caused the diabetes I must close this brief survey of the field of etiology, therefore, as I began it There is here no clue to the nature of diabetes

Diabetes is said to be incurable—once a diabetic, always a diabetic, yet there occurs a rare case that causes us to doubt the absolute infallability of this dictum Nearly fifty years ago Naunyn¹⁴ reported such a case "A four year old child, mother and older sister diabetic The patient's urine had been examined frequently for sugar and had always been sugar free The last examination was November 22, 1871 The child fell ill on November 26 with "Fibris gastrica acuta" November 27, night urine contained 5 8 per cent sugar, December 3, 3½ per cent sugar, December 8, 2 per cent sugar, December 13, it was sugar free Strict diet which had been instituted on November 27 was maintained for some time Then bread and milk were permitted Then when the urine continued to be free of sugar and the child continued to feel well and to flourish, the diet was made more liberal from time to time so that finally the child was permitted to take fruit, chocolate and puddings, and all the things that children like to eat The sugar never returned and the child developed into a healthy young woman who married at eighteen and had two healthy children In the course of twenty years no sugar had ever been found again" Priscilla White reported, "Fourteen, in a series

of 1,063 cases of juvenile diabetes, appeared to have spontaneously arrested diabetes. These cases were treated in no fashion different from the average diabetic child. They are now aglycosuric, eating freely, not taking insulin, and some have passed insurance examinations and tolerance tests ¹⁵ From time to time other clinicians have had the experience that after a more or less extended period a patient has been apparently cured and has been able on a most generous diet to go without insulin, only later, however, apparently to relapse. Many of us too have had the experience of finding that a patient admitted in diabetic coma and apparently with a severe diabetes would turn out to be an extremely mild diabetic. The most striking experience I have had, however, concerns a man of seventy-three who was admitted to Touro Infirmary, April 25, 1926. Diabetes had been discovered ten years previously. On April 4, 1926, he had found a small painful spot on his right foot. Four days later insulin was started and shortly after this the patient went into coma. The blood sugar was 190 mg per 100 cc. Under spinal anesthesia amputation was done at the middle third of the leg. On July 27, 1926, it was necessary to amputate the left leg because of gangrene. The patient had in the meantime been taking a diet of 100 carbohydrate, 40 protein and 150 fat, with 18 units of insulin a day, which controlled the glycosuria and kept the blood sugar between 95 and 125 mg per 100 cc. On November 27, 1928, he was admitted again because of pain in the pit of his stomach. He had been on a very low diet, he claimed that he took 32 carbohydrate, 50 protein and 60 fat ¹⁶, and 24 units of insulin daily. The patient vomited while in the hospital. On this admission traces of sugar were found in the urine and a trace of acetone, but no diacetic acid. The blood sugar was 200 and the CO₂ combining power of the blood 15.2 volumes per cent. In April 1929, he was admitted in a similar attack, the blood sugar being 325 and the CO₂ combining power 18. Each time it was necessary to increase the insulin temporarily, on the last occasion he received as much as 50 units in twenty-four hours, finally to return again to 24 units and his very low diet. On March 24, 1930, he was admitted with pain in his chest, head and shoulders, nausea and vomiting. Blood pressure was systolic 215, diastolic 90, falling subsequently to systolic 180, diastolic 70. An electrocardiogram taken March 31, 1930, and one on April 4, 1930, showed partial heart block, 4-3. On

March 26, 1930, the note was made Heart sounds vague and distant Rate slow but coupling not present Patient denies having taken medicine at home This question was asked because of the suspicion that he was taking digitalis March 29, coupling present, first beat comes in at 180, and disappears at 60, second beat appears at 160, and disappears at 70 March 31, pulse and heart rate continue to be about 44 The regular beats still seem to come in pairs On October 21, 1930, he was admitted because that morning at 1 30 a m he had been awakened by extreme cardiac pain and dyspnea There were many ectopic beats Heart rate was slow, 59 per minute Blood pressure, systolic 220, diastolic 122 An electrocardiogram showed partial A-V block, 2-1 In the meantime the patient had developed double cataracts during the four years he had been under observation When he was admitted again in September 1930, it was found that the blood sugar was normal (finding values of 91, 110, 86, 83 mg per 100 cc) and this without insulin The patient continued to take full diet including sweets During the time that we continued to observe him, to December 1930, he continued to have no glycosuria and no hyperglycemia On February 6, 1931, I received a letter from his wife saying that he had died January 26, 1931 Here then was a man who because of his diabetes had suffered gangrene of the right leg, and amputation, gangrene of the left leg, and amputation, several attacks of diabetic acidosis, cataracts of both eyes, coronary occlusion and heart block, and yet when he had reached the state of *sans* legs, *sans* eyes, and a badly damaged heart he was apparently not diabetic any longer

I summarize the field I have covered There is much evidence of disturbed function and very unsatisfactory evidence of organic change Are we, therefore, to look upon diabetes as a functional disease rather than as an organic one? May we hope some day to discover how the carburetor was put out of order, what put it out of order, and how we may restore it to normal function? It is along these lines, it seems to me, that diabetics may look confidently to the future

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HYPERPROTEINEMIA ITS SIGNIFICANCE*

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RECENT literature suggests that hyperproteinemia is not as rare as commonly believed. In addition, it has been shown that the presence of hyperproteinemia has not only considerable diagnostic significance, but explains many phenomena heretofore obscure.

It is the purpose of this paper to review the present knowledge concerning hyperproteinemia and to report thirteen additional cases. Interest in this subject was stimulated when it was discovered that persons with hyperproteinemia showed occasionally puzzling laboratory findings such as rouleaux formation of red blood cells, blood which could not be typed for transfusion and high blood calcium values.

Peters and Eisenman¹ and Osgood,² based on a study of many normal individuals, give 6 to 8 Gm per cent as the normal variation for total proteins with an albumin-globulin ratio varying from 1.43 to 1.72. By these accepted standards, a plasma protein of 8.00 Gm. per cent or over should be considered as evidence of hyperproteinemia.

Table I summarizes the total plasma protein determinations made by the clinical laboratories of the Boston City Hospital for the three-year period 1934 to 1936 inclusive. Of 557 determinations during 1934, only 0.2 per cent were over 8.00 Gm per cent as contrasted with 69.5 per cent which were less than 6.0 Gm per cent. During 1935, of 526 determinations, 1.1 per cent were higher than normal and 56.4 per cent less than normal. In 1936, 2.4 per cent of the protein determinations were over 8 Gm per cent and 49.2 per cent, were less than normal.

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Hypoproteinemia as a contributory cause of edema is so well appreciated that total plasma proteins are almost routinely determined when this condition is encountered. Edema has been in fact the main indication for the determination. This explains why more than 50 per cent of the values were less than normal.

TABLE I

Summary of Total Blood Protein Values Determined in the Clinical Laboratories of Boston City Hospital

| Year | Under 6.0 Gm % | | 6.0 to 7.9 Gm % | | 8.0 Gm % or over | | Total Determi- nations |
|------|-------------------|------|--------------------|------|---------------------|------|------------------------------|
| | Number | % of | Number | % of | Number | % of | |
| 1934 | 387 | 69.5 | 169 | 30.3 | 1 | 0.20 | 557 |
| 1935 | 297 | 56.4 | 223 | 42.5 | 6 | 1.10 | 526 |
| 1936 | 167 | 49.2 | 164 | 48.4 | 8 | 2.40 | 339 |

TABLE II

Clinical and Laboratory Data from Cases of Hyperproteinemia

| Case | Sex | Age | Diagnosis | Total Pro- tein grams % | Albu- min grams % | Globu- lin grams % | Fibrino- gen | Albumin- Globulin Ratio | Takata- Ara Reaction |
|------|-----|-----|-------------------------------------|-------------------------------------|----------------------------|-----------------------------|-----------------|-------------------------------|----------------------------|
| 1 | M | 55 | Multiple Myeloma | 12.2 | 3.2 | 8.4 | 0.60 | 0.38 | Positive |
| 2 | F | 50 | Multiple Myeloma | 10.6 | 4.5 | 5.2 | 0.78 | 0.84 | Positive |
| 3 | M | 63 | Multiple Myeloma | 9.4 | 3.7 | 5.2 | 0.42 | 0.71 | Positive |
| 4 | F | 74 | Multiple Myeloma | 10.8 | 1.2 | 9.6 | | 0.12 | Positive |
| 5 | M | 45 | Multiple Myeloma | 9.6 | 2.0 | 7.6 | 0.55 | 0.27 | Positive |
| 6 | F | 17 | Chronic Eczema | 8.6 | 5.1 | 3.5 | | 1.50 | |
| 7 | F | 59 | Multiple Myeloma | 9.6 | 4.0 | 5.6 | | 0.72 | Positive |
| 8 | F | 27 | Sarcoid of Boeck | 8.4 | | | | | Positive |
| 9 | M | 60 | Dehydration | 8.9 | | | | | |
| 10 | F | 67 | Multiple Myeloma | 11.0 | 3.0 | 8.7 | 0.26 | 0.34 | Positive |
| 11 | F | 14 | Otitis Media Dehy- dration | 8.1 | 3.5 | 4.5 | | 0.78 | |
| 12 | M | 40 | Hemolytic Jaundice ? Dehydration | 8.6 | 4.1 | 4.5 | | 0.90 | Negative |
| 13 | F | 34 | Lymphogranuloma Inguinale | 8.0 | 2.9 | 5.1 | | 0.56 | Positive |

In striking contrast are the few instances of hyperproteinemia. During and prior to 1934, a total protein value over 8 Gm per cent

was rarely encountered at this clinic. Its existence was not appreciated and blood protein determinations were consequently not requested in the conditions in which it is now known to occur. Early in 1935, the accidental discovery of hyperproteinemia led to the correct diagnosis of multiple myeloma, following which most of the persons suspected of having this disease were subjected to blood protein determinations. This accounts in the main for the marked increase in the number of instances of hyperproteinemia discovered during 1935 and 1936. Relevant data on these cases are briefly summarized in Table II. Clinical data were available on but eleven of the fifteen different cases of hyperproteinemia found in the laboratory records. (Two additional cases were obtained from the Evans Memorial Hospital.)

It will be noted that they are mostly instances of multiple myeloma, since in these hospitals at the present time, other causes of hyperproteinemia are either not generally appreciated or encountered.

DISEASES ASSOCIATED WITH HYPERPROTEINEMIA

(1) *Diseases Associated with Severe Dehydration*—Ever since Schmidt³ in 1850 reported high blood protein values (occasionally rising over 12 Gm per cent) in severe cases of cholera, it has been known that a markedly dehydrated state, regardless of the underlying mechanism producing it, could readily cause an elevation of the total blood protein above the accepted normal level. Marriott⁴ reported that increases of over 60 per cent in concentration of blood protein were common in infantile diarrhea and in rare cases the increase could be 100 per cent or more. Gamble⁵ showed that in dogs with artificial pyloric obstruction and vomiting, the total blood protein values increased. In one animal the value rose from 7.2 Gm per cent to 11.3 Gm per cent in forty-two hours.

Talbott⁶ in his study of heat cramps, (a disease characterized by severe dehydration) noted, not only elevated total blood protein values, which on one occasion reached 10.6 per cent, but also that the albumin-globulin ratio was reversed. The albumin concentration invariably was below 3.4 per cent while the serum globulin concentration increased from 2.5 to 7.4 per cent.

Because of their inability to traverse the normal capillary membranes, proteins are retained in the blood during hemoconcentration while fluid and electrolytes are lost.¹ Therefore, 100 cc of the con-

centrated blood would contain more protein than normally. By this reasoning one would expect all protein fractions to be equally affected by dehydration. It is generally believed that the albumin-globulin ratio in dehydration is not changed. That Talbott⁶ reports a lowering of albumin and an increase in globulin suggests that another factor besides hemoconcentration per se causes the high protein values found in heat cramps. The albumin molecule, being smaller than the globulin molecule, may traverse the blood vessel barrier if a decrease in capillary permeability occurs.¹ A combination during dehydration of capillary permeability change causing loss of the albumin fraction and hemoconcentration causing increase in the retained globulin fraction is one explanation for the findings reported by Talbott. In addition, there exists the possibility that in certain dehydrated states there is a stimulus for the formation of additional globulin. However, few studies of protein values in dehydration contain albumin-globulin ratios so one can only surmise how common may be this finding by Talbott.

Severe dehydration may occur in burns, heat cramps, diabetic acidosis, Addison's disease, intestinal obstructions and fistulae, severe diarrheas, diminished fluid intake and certain fulminating infections.⁷ It is important to bear in mind that diarrheas, intestinal obstructions and fistulae must be severe enough to cause rapid dehydration. These conditions when chronic prevent the absorption of protein and cause hypoproteinemia rather than hyperproteinemia.

(2) *Multiple Myeloma*—That multiple myeloma may be associated with hyperproteinemia is at present fairly well appreciated. In 1934, Foord,⁸ in reviewing the literature, collected eighteen cases and added three of his own. Since then other additional instances have been reported.^{9 10 11 12} This small number would seem to indicate that but a very minor percentage of cases of multiple myeloma can be expected to show high plasma protein values. However, the few available reports on hyperproteinemia are readily explained by Sweigert's statement⁹ that in only thirty-five of over 500 reported instances of myeloma were adequate quantitative investigation of plasma proteins completed. Of these thirty-five cases of myeloma in which the blood proteins were determined, twenty showed values of over 8.00 Gm. per cent. In a more recent survey of the literature, Gutman and Gutman¹² found thirty-five instances of hyperprote-

inemia among fifty-seven published cases of myeloma in which both blood protein and calcium determinations were made. These studies show that hyperproteinemia probably occurs in at least 50 to 60 per cent of cases of multiple myeloma and is a more valuable aid in the diagnosis than the finding of Bence-Jones protein in the urine.

That this finding is not rare is shown by our own figures. During a two-year period, seven cases were discovered in two Boston clinics (see Table 2) merely by routine determinations of blood proteins on cases in which this diagnosis was suspected. Foord⁸ observed three cases personally and Gutman et al¹³ noted this finding in four out of six cases of multiple myeloma. Recently Bing¹⁴ added fourteen cases to the literature.

TABLE III

Fluctuations in Blood Protein Level in Cases of Multiple Myeloma During Course of the Disease

| Case | Date | Total Protein grams % | Albumin grams % | Globulin grams % | Albumin-Globulin Ratio |
|------|----------|--------------------------|--------------------|---------------------|---------------------------|
| 7 | 2-25-36 | 6.2 | 3.1 | 3.1 | 1.00 |
| | 3-22-36 | 8.2 | 3.2 | 5.0 | 0.64 |
| | 3-31-36 | 7.1 | 2.7 | 4.4 | 0.60 |
| | 4-28-36 | 6.8 | 3.3 | 3.5 | 0.90 |
| | 7-24-36 | 8.8 | 3.6 | 5.2 | 0.69 |
| 4 | 10-31-36 | 9.6 | 4.0 | 5.6 | 0.72 |
| | 9-7-36 | 7.7 | 2.1 | 5.6 | 0.38 |
| | 11-4-36 | 9.8 | 2.0 | 7.6 | 0.27 |
| | 11-30-36 | 9.6 | 3.2 | 6.4 | 0.50 |
| | 12-29-36 | 9.7 | | | |

The blood protein level in multiple myeloma with hyperproteinemia is, however, not constant and may vary from time to time, occasionally diminishing, but tending on the whole to increase as the disease progresses. Figures taken from Cases number 4 and 7 (see Table III) show such variations in protein values. In Case number 7, the initial total protein was 6.8 per cent on February 25, 1936, increasing to 9.6 per cent on October 31, 1936. At two points the values fell back into the normal range only to rise again to a sustained high level for several months before death. In Case number 4, the

initial value was 7.7 Gm per cent on September 7, 1936, but rose rapidly to a hyperproteinemic level and remained there. Cantarow¹¹ and Bing¹⁵ have observed similar variations.

If the first blood protein value had been accepted as final, these cases could not have been included as instances of hyperproteinemia. This suggests the need for serial blood protein studies in all cases of multiple myeloma before the true incidence of hyperproteinemia can be determined. Similar variations in protein levels may possibly occur in other diseases associated with hyperproteinemia. Chester¹⁶ has shown that the blood protein level in myeloma cases could be increased by placing these patients on a high protein diet. Loss of protein through the kidneys and deficient nutrition are factors tending to counterbalance the tendency to hyperproteinemia.

Extraordinarily high protein values have been reported in this disease. A few values reaching to 16 Gm per cent are on record.^{17, 18} Values over 12 Gm per cent are common. The average total blood protein of twenty-one cases of hyperproteinemia in myelomatosis collected from the literature by Jeghers⁴ was 11.3 Gm per cent.

(3) *Lymphogranuloma Inguinale*—The extensive and pioneer studies of Gutman and his coworkers^{20, 12, 13} have shown that hyperproteinemia is commonly associated with lymphogranuloma inguinale. Twenty-six of thirty-five cases studied showed total blood protein values over 8.0 Gm per cent. The highest figure noted was 11.2 Gm per cent and there were ten instances of values exceeding 9.0 Gm per cent. In all cases, the albumin-globulin ratio was reversed with a marked increase in the globulin fraction. Fibrinogen was occasionally elevated to 0.6 Gm per cent, but in the majority of the cases was within normal limits. Dehydration as a cause for the hyperproteinemia was definitely eliminated.

The hyperproteinemia was more marked in those patients with chronic complications, particularly in females with rectal strictures. Although confirmatory studies are not available, the evidence presented seems conclusive. The one instance of this disease in our series showed a total protein value of 8.00 Gm per cent with a reversed albumin-globulin ratio. Since this disease is now known to be common in this country, it must always be considered where high blood protein values are found and confirmed by the Frei test. Conversely,

all persons with inguinal adenitis or rectal strictures should have blood protein studies as part of their diagnostic study

(4) *Sarcoid of Boeck*—Salvesen²¹ determined the blood proteins in three cases of sarcoid of Boeck. The values ranged from 9.00 to 9.69 Gm per cent, the increase being in the globulin fraction with the albumin-globulin ratio varying from 51 to 86. These high values were found to be consistent upon repeated determinations over a period of months. Salvesen believes that although the number of patients examined was small, the uniformity of results suggests that these changes are characteristic of this condition. The one case of sarcoid of Boeck found in our series confirms this contention. In Case 8 (Table II), this diagnosis was confirmed anatomically, the total protein was 8.4. Unfortunately, the albumin-globulin ratio was not determined. In one other case at the Boston City Hospital the total protein was normal but the albumin-globulin ratio markedly reversed. Bing¹⁴ included one case of sarcoid of Boeck in his series in which the globulin fraction was 6.2 Gm per cent of a total protein of 7.9 Gm per cent. In addition, he includes a case of erythema diutinum Bazin with hyperproteinemia, a disease believed by some to be related to sarcoid of Boeck.

Sarcoid of Boeck is probably a not uncommon disease in this country, judging by reported cases^{22, 23}. Unfortunately, none of these studies contain blood protein determinations. It is suggested that all cases of Boeck's sarcoid have such studies in the future. The finding of an unexplained hyperproteinemia may be the clue to an otherwise difficult diagnosis.

(5) *Leprosy*—The presence of hyperproteinemia in this disease is largely of academic interest in most parts of this country, since such cases are but rarely seen and then segregated as soon as the diagnosis is made. However, excellent blood protein studies are available. Frazier and Wu²⁴ in studying thirty-two cases noted that over 80 per cent showed an elevated total protein which averaged 8.7 Gm per cent. The highest value reached was 10.0 Gm per cent. The increase here was in the globulin fraction with the albumin-globulin ratio reversed. These results were found in the nodular, the maculonesthetic and mixed types of leprosy. Similar results are reported by Schlossman²⁵.

(6) *Kala-azar*—Sia and Wu²⁶ found hyperproteinemia in 40

per cent of the cases of Kala-azar which they studied. The highest total protein was 10.5 Gm per cent with a globulin value of 7.06 Gm per cent. Lloyd and Paul^{27, 28} found similar values. Since then this finding has been repeatedly confirmed^{29, 30}. In every case of Kala-azar on record in which the proteins have been investigated, there has been noted a marked increase in globulin, an absolute diminution of albumin and a reversal of the albumin-globulin ratio. Even the cases of Kala-azar without hyperproteinemia, have total protein values averaging 7.5 Gm per cent with a similar high globulin. These studies show that hyperglobulinemia is a constant feature in this disease and in about 40 per cent of the cases the globulin increase is sufficient to cause a true total hyperproteinemia. The fibrinogen levels in Kala-azar were not determined.

Lloyd and Paul²⁸ were able to show that the protein increase was almost entirely in the euglobulin fraction of the globulin. Values of euglobulin ten times the normal level were common. Following treatment, the protein values gradually returned to normal. The status of Kala-azar in the United States has recently been reviewed by Ginandes³¹.

(7) *Schistosomiasis*—That the blood protein values (especially the globulin) are elevated in this disease was first suspected when the globulin precipitation tests were found to be consistently positive. This led Meleney and Wu³² to study the protein fraction in a series of persons afflicted with *Schistosomiasis Japonica*. Fifty per cent were found to have total proteins over 8.00 Gm per cent, the highest value being 10.0 Gm per cent. The globulin fraction averaged 5.3 Gm per cent with a high value of 8.5 Gm per cent. The albumin-globulin ratio was invariably reversed, even in the cases with total protein values below 8.00 Gm per cent. Fibrinogen and subglobulin fractions were not determined. Following therapy with tatar emetic, the total blood proteins fell to a normal level, the albumin-globulin ratio also reverting to normal.

This disease, while rare in this country, continues to be the subject of periodic reports from the coastal cities^{33, 34}. The finding of high total protein values would be of great aid in the diagnosis of the chronic cases resembling portal cirrhosis, since in the latter condition protein values over 8.00 Gm per cent rarely occur.

(8) *Miscellaneous Diseases*—Hyperproteinemia occurs uncom-

monly in a few other diseases. Before assigning the cause to any specific disease entity, the factor of dehydration must be eliminated. In the future, as blood protein studies are performed more routinely, other diseases may be found to be associated with hyperproteinemia consistently enough to be included in the group already discussed. A suggestive syndrome which may fit in this category has recently been described by Bing and Neel.³⁵ They described two cases of hyperproteinemia with blood proteins of 10.8 and 11.3 Gm per cent respectively. These cases were unusual in that they presented no disease known to cause hyperproteinemia, but instead showed widespread changes in the central nervous system, especially in the cauda equina, radices and spinal cord, as well as spinal fluid changes. They presume the affection to be on a toxic-infectious basis, and believe the clinical picture not to have been described before. An additional case has since been published by these same authors.³⁶

It seems likely that sub-acute bacterial endocarditis will eventually be included in the group of diseases in which hyperproteinemia is characteristic. Kurten^{36, 37, 38, 39} while studying the formol-gel reaction in this disease, obtained positive results in thirty-three of thirty-five cases. A study of the protein fractions of the blood showed that all the cases with a positive formol-gel test had hyperglobulinemia. The total blood proteins averaged 8.4 Gm per cent, 50 per cent being over 8.00 Gm per cent and the range from 7.5 Gm per cent to 9.2 Gm per cent. The albumin fraction was invariably diminished averaging 1.9 Gm per cent. Hyperglobulinemia was present, the lowest value was 5.2 Gm per cent while the highest was 7.6 Gm per cent. These findings stimulated May,⁴⁰ and Troisier and co-workers⁴¹ to repeat this work. Unfortunately these latter investigators did not determine the protein values, but did show that the formol-gel reaction was positive in practically all cases of sub-acute bacterial endocarditis. The reaction should be done at a time when the patient's temperature is near normal. The general conclusion was that hyperglobulinemia was a constant enough feature of subacute bacterial endocarditis to be of diagnostic significance.

None of the standard American text books of medicine or reviews on this subject mentions the protein values. Although not adequately confirmed, protein determinations seem indicated in subacute bacterial endocarditis.

Loeper et al⁴² reported a case of a large malignant tumor of the kidney with a blood protein of 11.0 Gm per cent. Reiche⁴³ found an 11.4 Gm per cent total protein in a case of osteopathia osteopatra in a senile person. Gutman¹³ reported a miscellaneous group of cases with hyperproteinemia including two cases of lymphosarcoma, one of tuberculous lymphadenitis, one of portal cirrhosis as well as several undiagnosed diseases. Elevations of the total blood protein with reversal of the albumin-globulin ratio and characterized especially by marked increases in globulin have been reported in malaria,⁴⁴ myelogenous, leukemia,⁴⁵ lymphatic leukemia,¹⁴ syphilis,⁴⁶ rheumatoid arthritis,⁴⁷ filariasis,⁴⁸ trypanosomiasis⁴⁹ and tuberculosis.⁵⁰ However, it is extremely rare in these diseases for the total protein to be elevated above the level of 8 Gm per cent. In our own series, Case 6 (chronic eczema) and Case 12 (hemolytic jaundice), both showed an unexplained hyperproteinemia.

It should be appreciated that a protein level of 8.00 Gm per cent or over for the diagnosis of hyperproteinemia is only relative. In most cases, the terminology hyperglobulinemia would more truly fit the circumstances and probably include the cases with total values below 8 Gm per cent. Therefore, any total protein of 7.00 Gm per cent or over should be viewed with suspicion if the globulin is increased enough to cause marked reversal of the albumin-globulin ratio. It is evident that the determination of blood proteins should always include an albumin-globulin ratio in addition to the total protein.

NATURE OF THE PROTEIN INCREASE

Normal blood protein consists of a globulin, albumin and fibrinogen fraction, the globulin fraction being composed of euglobulin, pseudoglobulin I and pseudoglobulin II. Theoretically, we might expect hyperproteinemia to result from an increase of any or all of these various fractions. Actually, with a few rare exceptions, the protein increase is usually limited to one special fraction.

Fibrinogen normally varies from 0.2 to 0.4 Gm per cent and constitutes only 3 to 6 per cent of the total protein.² Therefore, increases of even several hundred per cent in this fraction would have but slight effect on the total protein. An increase in the fibrinogen fraction is called hyperfibrinosis. Values over 1.0 Gm per cent are extremely rare and only in the case reported by Reimann⁵¹ was it suffi-

ciently elevated to be the chief cause of the hyperproteinemia. In this instance, the fibrinogen was 5.48 Gm per cent with a total blood protein of 10.12 Gm per cent. While marked degrees of hypernephrosis are rare, it is not unusual in hyperproteinemia to find increases in its fibrinogen fraction varying from 0.5 to 0.8 Gm per cent. In the series herein reported, fibrinogen was increased in three out of five cases in which this determination was made. Of the multiple myeloma cases on record, about half have increased fibrinogen values. Gutman and his coworkers¹³ noted high fibrinogen (not over 0.6 Gm per cent) in about 30 per cent of their cases of lymphogranuloma inguinale in which this determination was made. Fibrinogen has not been determined in other diseases associated with hyperproteinemia.

Therefore, in hyperproteinemia it is desirable to determine the fibrinogen value if possible. While an increase in this fraction is not responsible for the increase in total protein, it is quite likely to be one of the causative factors in producing some of the puzzling phenomena associated with hyperproteinemia. These will be discussed later.

The albumin fraction of the blood normally varies from 4.0 to 5.8 Gm per cent¹ and an increase is practically never the cause of the hyperproteinemia. In a review of the available literature, only one instance of an albumin fraction greater than the upper limit of normal was found. Bennold⁶² reported a case of multiple myeloma in which the albumin fraction was 6.2 Gm per cent. Even here the albumin-globulin ratio was reversed since the globulin fraction was 7.9 Gm per cent.

In hyperproteinemia, the albumin fraction is invariably decreased, regardless of the disease producing the increase in total protein. In the cases reported in this paper, the average albumin fraction is 3.4 Gm per cent. In twenty-one cases of hyperproteinemia associated with multiple myeloma collected from the literature the average albumin was 2.9 Gm per cent. In the lymphogranuloma inguinale cases reported by Gutman and coworkers, the albumin fraction averaged 3.6 Gm per cent with no value higher than 4.7 Gm per cent. Talbott⁶ noted that the albumin was invariably below 3.4 Gm per cent in his cases of dehydration associated with heat cramps. Similar low values for albumin are almost constantly found in leprosy,²⁴ Kala-azar,²⁸ sarcoid of Boeck²¹ and schistosomiasis.³² The signifi-

cance of this drop in albumin in the presence of hyperproteinemia will be discussed later in regard to the oncotic pressure of the blood

In contrast to the fairly common finding of Bence-Jones proteinuria in multiple myeloma, the demonstration of Bence-Jones protein in the blood is only rarely accomplished. To find this protein in the blood in amounts sufficient to cause hyperproteinemia is a rarity worthy of individual case reports. Cantarow,¹¹ in reviewing the literature on this subject, points out that the combination of hyperproteinemia and Bence-Jones proteinemia has rarely been conclusively demonstrated. Besides Cantarow's case, there are but two others on record.^{53, 54} These findings have only been recorded in instances of multiple myeloma. Bence-Jones protein is not associated with other diseases causing hyperproteinemia. The failure to demonstrate more often the presence of Bence-Jones protein in the blood when it is known to be present in the urine, may be due to chemical difficulties associated with the identification and isolation of this protein. It seems likely that under rare circumstances, Bence-Jones protein may accumulate in the blood in sufficient amount to be responsible for a hyperproteinemia. Since Bence-Jones protein is immunologically distinct from normal blood proteins, Perlzweig and his coworkers⁵⁵ proposed the idea that the Bence-Jones protein formed in the body stimulated hyperproteinemia in the same fashion that foreign protein or bacteria caused such a response in animals which were being immunized. Sweigert⁹ believes this hypothesis untenable since hyperproteinemia usually occurs independently of Bence-Jones protein or may, in rare cases, actually be due to a Bence-Jones proteinemia.

Except for the rare instances previously mentioned, hyperproteinemia is due to an increase in the globulin fraction above the normal upper limit of 2.5 to 3.0 Gm per cent.¹ The average figures for the constituents of the normal globulin fraction are usually given as euglobulin 0.7 Gm per cent, pseudoglobulin I, 0.94 Gm per cent, and pseudoglobulin II, 0.68 Gm per cent.⁵⁶

Gutman and his coworkers¹³ found that in lymphogranuloma inguinale the hyperproteinemia was due to an increase in the euglobulin and pseudoglobulin I fractions. Rises in euglobulin were striking but not constant, the highest value being 4.0 Gm per cent. Pseudoglobulin I was increased in all cases, 3.3 Gm per cent being the

highest value. In Kala-azar^{23 29} and leprosy,²⁴ the increase of the protein is usually in the euglobulin fraction.

In multiple myeloma, the protein increase may be in any one or more of the subglobulin fractions. Jacobson⁵⁷ found the euglobulin fraction to constitute the bulk of the globulin in three cases of myeloma with values reaching to 10.00 Gm. per cent. In two other cases, the pseudoglobulin fractions were highest with a figure of 5.8 Gm. per cent. in one instance. Gros,¹⁰ in two cases, found the euglobulin to be normal and both pseudoglobulin fractions to be increased from two to six times the normal values. However, these are unusual findings. The majority of cases of multiple myeloma with hyperproteinemia show marked rises in euglobulin with figures varying from 4.1 to 8.0 Gm. per cent. with only slight or no increase in the pseudoglobulin fractions.

Subglobulin fraction determinations are not available in cases of dehydration⁶ or Boek's sarcoid²¹. It can be concluded that euglobulin and more rarely pseudoglobulin I constitute the bulk of the protein increases responsible for the majority of the instances of hyperproteinemia.

In a recent review, Reimann, Medes and Fisher⁵⁸ conclude that the mechanism of the formation of blood proteins is still an unsolved problem. Several attempts have been made to see if a study of hyperproteinemia would aid in the elucidation of this problem^{9, 55}. That the bone marrow may be the source of the blood proteins is suggested by the frequent finding of hyperproteinemia in multiple myeloma, a disease in which the bone marrow is involved⁵⁵. However, equally marked degrees of hyperproteinemia may be found in diseases with no pathological change in the bone marrow. Fibrinogen, a hepatic product, is often increased. Sweigert⁹ concluded that the whole subject is vague and more information is needed. Not only does a study of hyperproteinemia fail to solve the mechanism of the formation of proteins, in general, but leaves the subject even more confused.

PATHOLOGIC PHYSIOLOGY OF HYPERPROTEINEMIA

Unusual phenomena due to the presence of hyperproteinemia are encountered frequently, one or more being present in practically every case. Recent studies have done much to clarify the mechanism underlying several of the more interesting ones. An understanding

of these may occasionally be of great diagnostic aid by indicating the probable presence of an abnormal blood protein level. In most instances, the phenomena seem to depend primarily on an increase in the globulin of the blood with the fibrinogen fraction playing a lesser role. The capricious character of these phenomena must be borne in mind, since they may be present in some cases and absent in others even though the blood chemistry of each is approximately the same. This suggests disturbances in basic physical-chemical mechanisms of the blood still to be elucidated.

(1) *Rouleau Formation.*—Abnormally rapid and marked rouleau formation (auto-hemagglutination) of red blood cells has been observed frequently in cases of hyperproteinemia. Reimann⁵¹ and Foord⁸ in particular, have stressed its significance. McCombs and McElroy⁵⁰ recently pointed out that the term auto-hemagglutination as introduced by Reimann⁵¹ is wrong and that pseudo-agglutination is the correct expression for rouleau formation. They suggest that auto-hemagglutination be used only for cold agglutination. However, Reimann's terminology is now widely used.

This phenomenon is most frequently noted (1) when making blood smears, (2) in the red blood cell pipette, or in the counting chamber while performing an erythrocyte count, (3) when attempting to type blood for a transfusion, and (4) during the performance of an erythrocytic sedimentation rate.

In addition to these, Foord⁸ suggests that the possibility of intravascular auto-hemagglutination must be considered. In one case reported by him, this phenomenon was observed in the retinal veins during ophthalmoscopic examination when the circulation was slowed by firm pressure on the eyeball. When the venous flow was very sluggish, large red granules slowly following one another along the course of the veins were seen, resembling the aggregates seen in the sedimentation tubes. Foord further suggests that the unusual clinical features in the cases of multiple myeloma with hyperproteinemia reported by Wintrobe and Buell⁶⁰ might be explained on the basis of such capillary obstruction. Wintrobe and Buell noted in their patient mottling of the skin on the extremities, blueness and later coldness and blanching of the acral regions, and finally bilateral thrombosis of the retinal veins. Fahraeus⁶¹ believes rouleau formation occurs in the streaming blood and that its presence may have greater

pathologic importance in disease than commonly believed. He was able to show that greater pressure was necessary to force blood containing clumped red blood cells through narrow glass capillary tubes than when the blood was normal and the red blood cells not aggregated.

Rouleau formation is due to changes in electric charge resulting from an alteration of the albumin-globulin ratio and an increase in globulin or fibrinogen or both.⁶¹ Since marked increases in globulin and occasionally lesser increases in fibrinogen are constant in most cases of hyperproteinemia, it can be appreciated why this phenomenon is frequently encountered.

Of particular interest is the phenomenon of auto-hemagglutination in relation to blood transfusion. If the patient's plasma is abnormally rich in globulin or fibrinogen, prompt rouleau formation of all foreign red blood cells may occur regardless of whether they are of the same blood group or not. Case 4 in our series showed this to a striking degree. Auto-hemagglutination occurred with the blood of every one of over twenty donors of the same type on cross matching the blood prior to transfusion. Because of the urgent need, this patient was given several transfusions of blood which showed rouleau formation on cross matching. No harmful effects were observed. The rouleau formation of the donor's red blood cells in the recipient's plasma should be differentiated from rouleau formation of the patient's red blood cells in his own plasma. It is the latter type which causes intravascular aggregation of red blood cells.

It is also important to distinguish the clumping of erythrocytes due to auto-hemagglutination from that due to true iso-agglutination (clumping due to blood from a different blood group). Abnormally rapid rouleau formation disappears on slight dilution of the blood, whereas in iso-agglutination, this is not true.⁹ Microscopic examination will show the orderly rouleau formation in auto-hemagglutination in contrast to the amorphous, disorderly clumping of incompatible bloods due to iso-agglutination. In addition, true iso-agglutinins may be removed from the serum by absorption.

If the patient needs a transfusion, it seems reasonably safe to give blood which shows rouleau formation with the recipient's plasma provided the donor's blood is of the proper group and well diluted with saline. Motion within the vascular channels will further aid in lessening this type of rouleau formation.⁸ Diluting with saline may

be necessary to count the red blood cells if clumping due to rouleau formation is marked.

(2) *Increased Sedimentation Rate*—It has been a frequent observation that the sedimentation rate of the erythrocytes may be markedly increased in the presence of hyperproteinemia^{8, 62, 63}. In Reimann's case,⁵¹ complete settling of the red blood cells occurred in ten minutes, and large macroscopically visible clumps were seen even before settling was complete. Freund and Magnus-Levy,⁶² and Sweigert⁶ have commented on this phenomenon and pointed out that it should immediately suggest the possibility of hyperproteinemia. Its presence was noted in cases of lymphogranuloma inguinale with hyperproteinemia²⁰. In our own cases, striking increases in sedimentation rate were noted in all the cases of multiple myeloma in which it was performed. The rates varied from five to twenty times the usual figure expressed in millimeters fall per minute. Several different techniques were used.

That the increased rate does not depend on infection per se is shown by the fact that the highest rates have been in cases of multiple myeloma, a disease in which infection does not play a primary role. Gilligan and Ernstene⁶³ were able to show that in most diseases the sedimentation rate varied directly with the fibrinogen level. The greater the plasma fibrinogen content, the greater the size of the settling red cell aggregates with a consequent greater speed of erythrocytic sedimentation. They did not, however, include cases of hyperproteinemia in their study. In hyperproteinemia, fibrinogen values are often normal, and when increased, only moderately so. That the globulin level plays a minor role in controlling the rate of sedimentation is also known⁵⁴. Bendien and Snapper⁶⁵ have shown that the relation between the factors increasing the sedimentation rate can be expressed in the following manner:

$$\text{Sedimentation Rate} = \frac{45}{\text{cell volume}} \times [(\text{Fibrinogen \%} - 3.5) \times 12 + (\text{globulin \%} - 22 \times 2.5)]$$

It is thus evident that the marked globulin increases causing hyperproteinemia can significantly increase the sedimentation rate. Reimann⁵¹ has shown that both globulin and fibrinogen increases could aggregate red blood cells.

(3) *Spontaneous Precipitation of Blood Proteins*—In the cases

in which Bence-Jones proteinemia was present, protein precipitation in the serum, especially during inactivation for the Wassermann reaction at 56° C has been observed^{11, 60 67, 71} Wintrobe and Buell⁶⁰ reported a case of hyperproteinemia associated with multiple myeloma which is unique in that the blood contained an abnormal protein which precipitated spontaneously, even when the blood was drawn with precautions to prevent changes in temperature, and alterations in hydrogen-ion concentration from loss of carbon dioxide. The physical state of this protein in the body was not discovered since it was never obtained in solution in the blood.

The precipitate was a dense yellow viscous mass which after purification was coagulated in faintly acid solutions at 40° C, but did not disappear on boiling. This protein, which differed from the usual type of Bence-Jones protein both in its insolubility and its behavior towards heat, was associated with neither significant kidney damage nor Bence-Jones proteinuria, and was contained in the globulin fraction.

Karlins and Lundquist⁶⁷ described their experience with a blood treated with trichloracetic acid. In their case, a fine, milky precipitate appeared just above the layer of blood cells, almost equal in volume to the blood cells. The precipitate dissolved when washed with heated water but did not reappear on cooling. It precipitated, however, on adding sulphosalicylic acid, disappeared on boiling and reappeared on cooling.

(4) *Blood Protein Precipitation by Hayem's Solution*—Jacobson⁵⁷ and also Bonninger⁶⁶ have observed that immediately after mixing blood from patients with hyperproteinemia due to multiple myeloma with Hayem's solution, prior to performing a red blood cell count, a coarse, white precipitate formed. This same precipitate resulted whether serum or plasma were used. Even 1:250 dilutions of serum showed this phenomenon. Jacobson was able to show that the material precipitated by Hayem's solution was neither Bence-Jones protein nor the pseudo-globulin fraction but contained in the euglobulin fraction. The 0.25 per cent bichloride of mercury present in Hayem's solution proved to be the precipitating agent. This is extremely interesting in view of the strongly positive flocculations obtained when the Takata-Ara reaction (in which bichloride of mercury is a constituent) is performed on bloods with elevated blood

globulins These observations suggest that this phenomenon can be expected in any case of hyperproteinemia in which the euglobulin fraction is increased Diluents for the red blood cell count which do not contain mercuric bichloride will not precipitate the blood protein

(5) *Discrepancy in Acid-Base Equivalence*—Gutman and his coworkers¹³ state that in the determination of serum electrolyte partitions in normal persons by their methods, the total determined base usually exceeds total determined acids by 1 to 4 milli-equivalents per liter, i.e., B-A is rarely negative (where B represents total base and A total acids) It appeared from their data that in most cases of hyperproteinemia with definite hyperglobulinemia, irrespective of the etiology, there was an apparent excess of total determined acid equivalents over total base, i.e., B-A appeared to be negative This apparent discrepancy could be exhibited in every case in which the euglobulin fraction of the blood protein exceeded 14 Gm per cent, the discrepancy becoming more marked as the euglobulin fraction increased, showing an approximately linear relationship

Examination of the individual electrolyte components of the blood, other than protein, showed no obvious deviation from the normal in most of these cases These workers believe that the discrepancy in acid-base equivalence observed by them is apparent only and not real They point out that the error is introduced by the application to pathologic serum globulin (containing an excess of abnormal euglobulin) of a factor for calculating base bound to globulin which was derived from normal serum globulin They suggest that a correction of the factor ordinarily used to calculate base bound to globulin is necessary when that factor is applied to sera with markedly increased globulin content

(6) *Relation of Hypercalcemia to Hyperproteinemia*—The formula (total calcium = -0.255 phosphorus + 0.566 protein + 7) expresses the relation which exists between calcium and protein of the blood when the latter is at low or normal levels⁶⁹ It is well known that normally about 50 per cent of the serum calcium exists as a non-diffusible fraction bound to the blood protein⁷⁰ On this evidence it is generally stated that a rise in the blood proteins should be accompanied by an increase in the blood calcium^{69 70} Seeming support to this contention can be found in the frequent reports of the presence

of hyperealeemia in multiple myeloma associated with hyperproteinemia^{8 15 12 9}

Recent work by Gutman and Gutman¹² has shown this viewpoint to be erroneous. These workers state that hyperproteinemia is not a cause of hyperealeemia nor responsible for it, that there is no proportionality between total serum protein and serum ealeium levels, and that no inference as to the ealeium content of the blood can be drawn from the total protein content. They support their conclusions with the following data. Of thirty-five reported cases of multiple myeloma with hyperproteinemia, hyperealeemia was present in only twenty-three, whereas in eighteen cases of multiple myeloma, hyperealeemia was associated with normal or low serum proteins. In a group of cases with hyperproteinemia such as lymphogranuloma inguinale, lymphosarcoma, tuberculosis, etc., in which bone destruction did not exist, hyperealeemia was not found¹². In those cases of multiple myeloma in which hyperealeemia was found in conjunction with hyperproteinemia, the ealeium increase may well have been due to co-existing bone destruction by neoplastic tissue. Therefore, they conclude that it is probable that the increase in the protein-bound calcium fraction is a result and not a cause of the hyperealemia, for the ratio of diffusible ealeium to total ealeium remained reasonably constant whether the serum protein was increased or normal.

Cantarow¹¹ likewise does not accept that hyperealeemia in multiple myeloma is due to hyperproteinemia. He suggests the possible existence of a state of secondary hyperparathyroidism, the excessive mobilization of ealeium from involved areas of the skeleton, and the presence of marked renal functional impairment and acidosis as complicating factors which may influence the ealeium level in this disease.

(7) *Failure of Clot to Retract*—Another unusual hematologic phenomenon found in some cases with hyperproteinemia is failure of retractility of the blood clot. Cition⁷¹ observed this reaction in a case of multiple myeloma, but its association with hyperproteinemia was first noted by Perlzweig⁶⁵ who found it practically impossible to obtain serum for blood calcium determinations because of failure of the clot to retract, even on prolonged and repeated centrifugalization. Serum was finally obtained by expressing it mechanically from the clot. Reimann⁵¹ reported a similar experience. Foord⁸ noted that in a sample of 4 cc. of whole blood in a test tube, the cells settled

promptly while the supernatent fluid formed a jelly-like mass which did not contract in forty-eight hours, and after much manipulation only one-half cc of serum could be expressed.

An acceptable explanation for this phenomenon has not yet been proposed. Perlzweig⁵⁵ suggested that it might be due to an excessive amount of fibrinogen in the blood, which was so in his case, and especially in the instance reported by Reimann⁵¹. However, in Hubbard's case⁷² and in one of our own (Case 1, Table 2) the blood fibrinogen values were as high as that reported by Perlzweig, yet no unusual behavior of the clot was observed.

(8) *Rapid Coagulation of Blood*—Rapid coagulation of the blood has been frequently observed.^{71 73 74} In Citron's case⁷¹ the blood clotted immediately upon withdrawal and even the use of magnesium sulphate, an anti-coagulant, could not prevent it. Johansen⁷³ was able to prevent unduly rapid coagulation of the blood in his case only by using three times the usual amount of anti-coagulant. In one case in our series (Case 2, Table 2) the blood clotted before it could be emptied from the syringe. At first this was believed to be due to slow technique. Repeated attempts to obtain whole blood were successful only when the anti-coagulant was placed directly in the syringe before the blood was drawn. The explanation of this phenomenon is not clear. Citron⁷¹ found the platelet count to be normal. Since fibrinogen and calcium play important roles in the clotting mechanism, their relation to rapid coagulation may be postulated. In our case, the fibrinogen was increased to 0.78 Gm. per cent, but in other cases with equally high values rapid coagulation has not been noted. Many cases of hyperproteinemia with hypercalcemia in multiple myeloma have had normal clotting time. Rapid coagulation of blood has been noted only in instances of myelomatosis with high protein values.

(9) *Oncotic (Osmotic) Pressure of the Blood*—It is well known that in hypoproteinemia the oncotic pressure of the blood is below normal and transudation of fluid to tissues occurs with the formation of edema. Conversely, in hyperproteinemia, one would expect the oncotic pressure to be greater than normal. If this were true, it could counteract the filtration pressure in the kidney, lead to nitrogen and water retention, and cause hydremia in the blood stream.

Several studies are available of the actual oncotic pressure ex-

erted by the increased total protein^{53 6 20} The values were all found to be normal No evidence for hydremia was presented This apparent discrepancy between the theoretical consideration and practical findings is easily explained Normally, the high level for the oncotic pressure of the blood is less than 400 mm of water One gram of albumin exerts a colloid oncotic pressure of 75 mm of water whereas an equal amount of globulin has a colloid oncotic pressure of only 19 mm of water⁷⁶ The value for fibrinogen is so small that it can be disregarded for practical considerations These pressures are directly correlated with the smallness of the size of the molecules The minimum "molecular weight" of serum albumin is about 45,000, of pseudoglobulin 81,000, and euglobulin 135,000, while that of fibrinogen is even higher⁷⁶ In practically every case of hyperproteinemia on record, the albumin fraction is found to be reduced while the globulin fraction is increased Since albumin exerts four times the osmotic effect of globulin, a rise of four grams of globulin compensates for a drop of one gram of albumin This drop in albumin thus compensates for the globulin increase and explains why the oncotic pressure of the blood remains normal in hyperproteinemia

(10) *Anticomplementary Wassermann Reactions*—The occurrence of anticomplementary Wassermann reactions in myelomatosis with hyperproteinemia has been reported by Citron,⁷¹ Kleine,⁷⁰ Hallermann,⁷⁷ Magnus-Levy,⁷⁴ and Bing^{14, 15} Williams and Gutman^{20, 78} have recently suggested that the hyperproteinemia commonly found in lymphogranuloma inguinale may account for the falsely positive and repeatedly anticomplementary Wassermann reactions reported in the literature for this disease⁷⁹ and encountered in several of their own cases These investigators⁷⁸ noted that the Wassermann reaction was reported as anticomplementary in 22 per cent of seventy-four Frei-positive patients as compared to approximately 1 per cent in the general hospital population It was further noted that the same phenomenon was present in two of three cases of myelomatosis with hyperproteinemia but not in four cases without elevated blood proteins They observed also, similar anticomplementary Wassermann reactions associated with hyperproteinemia in occasional cases of tuberculous adenitis, nonspecific infections, lymphosarcoma and pregnancy Of interest are reports of several cases of Boeck's sarcoid with positive Wassermann reactions^{80 23} Hyperglobulinemia may explain

the false positive Wassermann reactions commonly found in subacute bacterial endocarditis⁸¹ Brahmachari was able to prevent hemolysis in a complete hemolytic system by the addition of euglobulin from Kala-azar blood^{81, 82, 83} Gutman and Williams⁷⁸ state that there is evidence, presumptive and experimental, that one of the important factors associated with nonspecific fixation of complement in man, is increased serum globulin, particularly in the euglobulin fraction This reaction was not observed in our series of cases since the Kahn and Hinton tests were performed routinely instead of the Wassermann reaction It is best to check all doubtful Wassermann reactions in cases of hyperproteinemia by means of the Kahn, Hinton or similar procedures

(11) *Renal Function*—The occurrence of atypical nephritis with and without evidence of renal failure has been frequently observed in multiple myeloma associated with hyperproteinemia^{8, 9, 15} This raises the question as to whether hyperproteinemia per se is responsible for it Excluding incidental renal changes, and complicating true nephritides, the cause of the abnormal renal findings in myelomatosis with hyperproteinemia have been attributed to three possible mechanisms (1) tubular atrophy due to obstruction of the tubules by casts of Bence-Jones protein, (2) plugging of the glomerul by the precipitation of thick protein and (3) functional obstruction of the glomerular capillaries as a result of intravascular auto-hemagglutination⁸ Amyloidosis as a result of myelomatosis rarely involves the kidney to any marked degree Variations in oncotic pressure do not occur in hyperproteinemia and therefore this factor cannot affect renal function There have been no studies specifically correlating renal function and hyperproteinemia other than in multiple myeloma, so a generalized conclusion is not at present possible However, impaired renal function is not a prominent feature in the other diseases commonly associated with hyperproteinemia except possibly in dehydration

(12) *Miscellaneous*—Studies of other physical-chemical phenomena of the blood in hyperproteinemia may be important if the meager data available is confirmed Lloyd and Paul²⁸ found an increase in the pH of the blood in Kala-azar from an average normal of 7.37 to 7.40 By Sorensen's method, they showed the iso-electric point of Kala-azar serum to be 4.30 as compared to a normal of 4.73

They found these results to be consistent and correlated with the increases in globulin. Perlzweig and his co-workers⁵⁵ were unable to draw any conclusions regarding surface tension of the blood in hyperproteinemia, but reported a suggestive increase. Wintrobe and Buell⁶⁰ noted that the viscosity of the blood seemed to be increased in their ease but offered no measurements. Bonninger⁶⁸ and Bing¹⁴ found the serum which oozed out of the blood clot in their cases to be very viscous and sticky.

SIMPLIFIED PROCEDURES FOR DETECTING HYPERPROTEINEMIA

Unfortunately, the determination of total blood protein and albumin-globulin ratio is a complicated technical procedure which will prevent its use in a routine fashion whenever the presence of hyperproteinemia is suspected. Attempts have been made to devise simplified procedures for detecting protein increases. Since with rare exceptions the protein increase is in the globulin fraction, any test which will detect hyperglobulinemia should theoretically be a good method for detecting hyperproteinemia. That globulin increases are easily detected is well shown by the surprising number of tests which have been devised for this purpose. Bing¹⁴ has recently reviewed all the simple methods for detecting globulin increases and discussed their relative merits. These procedures include: The Takata-Ara reaction, Brahmaehall's precipitation test, Ray's hemolytic test, Sia's globulin precipitation test, Napier's aldehyd test, formol-gel reaction, Chopra's urea stibamin test, formol-stibosan reaction, sulpharsenol reaction, Bauer's magnum chlorid flocculation reaction and Henry's melanin flocculation reaction.

Of these procedures, three (Takata-Ara reaction, formol-gel reaction and Sia's globulin precipitation test) are well enough standardized to be used. While their true status can only be determined by further studies, the successful results already recorded warrant their use by those who lack better laboratory facilities. A positive result by one of these procedures indicates that the globulin is abnormally increased and calls for the determination of the blood proteins by chemical analysis. When all three tests are negative, it is quite unlikely that hyperproteinemia exists. This will save determining the blood proteins in many instances.

(1) *Takata-Ara Reaction*—The extensive literature available

concerning this test has been recently reviewed by Kırk,⁸⁴ who pointed out that positive tests are found in any disease causing an elevation of the globulin fraction of the blood over 3.00 Gm per cent and a reversal of the albumin-globulin ratio

The technical details of this test are described elsewhere^{19, 85} They consist essentially of the following Six small test tubes are used containing respectively 1/2, 1/4, 1/16, 1/32, 1/64 and 1/128 dilutions of blood serum in normal saline To each tube are added 0.25 cc of a 10 per cent solution of sodium carbonate and 0.15 cc of 0.5 per cent mercuric chloride solution The contents of each tube are well mixed A positive reaction is present when a definite, pearly, flocculent precipitate persists in one or more tubes at the end of eighteen to twenty-four hours

Jeghers¹⁹ and Gros¹⁰ have noted markedly positive Takata-Ara reactions in each of five cases of multiple myeloma associated with hyperproteinemia An unusually heavy precipitate formed which was often present in all tubes and of greater amount than the positive results in portal cirrhosis

In the cases of hyperproteinemia reported in this paper (Table 2), the Takata-Ara was positive in all cases in which it was performed except one The negative result occurred in a case of hemolytic jaundice Other laboratory data in this instance suggested hemoconcentration The ratio was only slightly reversed (0.9) with the albumin 4.1 and the globulin 4.5 Gm per cent In each case of multiple myeloma the test was markedly positive

Salvesen²¹ reported positive Takata-Ara reactions in his cases of Boeck's sarcoid with hyperproteinemia Where the test was performed, Williams and Gutman²⁰ noted positive results in cases of lymphogranuloma inguinale with hyperproteinemia Hugonot⁸⁶ reported the test positive in cases of Kala-azar

Since the precipitate formed in a positive Takata-Ara reaction is believed to depend on an increase in the globulin fraction and a diminution in the percentage of albumin, it is understandable why a strongly positive test should result in cases of hyperproteinemia As already pointed out, not only does the globulin increase in hyperproteinemia, but the albumin is commonly diminished It is not known at present how this test will behave if the protein increase is

in the albumin, fibrinogen or Bence-Jones protein. However, these occur so rarely that they should receive little practical consideration.

(2) *Formol-Gel Reaction* — The formol-gel reaction is also known as the Gaté and Papacosta's reaction, Fox and Mackie's reaction and Kurten's reaction.¹⁴ This reaction depends upon gel formation when formalin is added to blood serum. The whitening of the serum or gel which occurs sometimes is the basis of Napier's aldehyd test.⁸⁷ Bing¹⁴ has recently standardized the formol-gel reaction and advised the following technique: a 36 per cent formalin solution is employed which should be neutralized with sodium hydroxide. The reaction is much slower if the solution is acid. Two large drops of the neutralized formalin solution are added to 1 cc. of serum in a small test tube. It is important that serum and not plasma be used, since the fibrinogen in the latter can give a false positive reaction. The material is mixed and allowed to stand at room temperature for three hours. The reaction is considered positive only if gelification is complete and the tube can be inverted without losing the contents. The presence or absence of a white opacity is not important by this technique. The more the globulin in the serum is increased, the sooner the gel formation is completed. Bing reported complete gelification within fifteen seconds to five minutes in some of his cases of hyperproteinemia. In all cases, gelification occurred within three hours. If no gel is formed by the end of three hours, the test is considered negative.

The formol-gel reaction has been widely used in tropical countries in the diagnosis of Kala-azar and schistosomiasis. The positiveness of the reaction has been shown to be related to the hyperproteinemia, more specifically the hypereuglobulinemia, associated with these diseases. Lloyd and Paul,^{27, 28} in their studies in Kala-azar, deduce that the formol-gel reaction is of a double nature, one factor being specific and associated with the high euglobulin fraction of the blood serum, the other being nonspecific and analogous with complement-fixation, though not identical with it as serologically understood, for they could not prevent the formol-gel reaction by inactivation of the whole serum. They have shown further that in those cases of proved Kala-azar with a normal albumin-globulin ratio and a positive formol-gel reaction, the euglobulin fraction made up 40 to 50 per cent of the total globulin. The formol-gel reaction fades slowly as the euglob-

ulin value approaches normal, and is completely extinguished when euglobulin comes within normal limits

This test should have wide application in the diagnosis of all types of hyperproteinemia since the protein increase in the vast majority of the cases is in the euglobulin fraction. Bing,¹⁴ in particular, has presented much evidence to favor the use of the formol-gel reaction for detecting hyperproteinemia. This test was not tried on any of the cases herein reported.

Bing¹⁴ found the formol-gel reaction to be strongly positive in each of the thirty-one cases with hyperproteinemia of varied etiology, but negative in a solution of horse-globulin and in serum from normal subjects and patients with other affections. Sweigert⁹ likewise found this test of value in detecting hyperproteinemia in a patient with multiple myeloma.

(3) *Globulin Precipitation Test*—This test, popularized by Sia,⁸⁸ has been found to be almost uniformly positive in cases of Kala-azar and schistosomiasis. Ray's "hemolytic" test,⁸⁹ used for the same purpose, depends upon a similar globulin precipitation for a positive result.

The technique is simple.⁹⁰ Twenty cubic millimeters of blood (measured with a Sahl¹ hemoglobin pipette) is collected from a puncture wound in the finger and immediately expelled into 0.6 cc. of distilled water in a small test tube. All apparatus should be scrupulously clean. The contents of the tube are quickly mixed by rotating and shaking several times. The tube is then allowed to stand without further shaking. Readings are made at the end of five, fifteen, thirty and sixty minutes.

In a positive test, there is at first a uniform haziness or turbidity, the degree being directly proportional to the amount of precipitable globulin present in the blood. The degree of turbidity is read at the five-minute period. Gradually, the turbid material precipitates to the bottom of the test tube. Complete sedimentation at the end of fifteen minutes is considered a ++++ positive reaction, at thirty minutes a + + + and at sixty minutes a + + or + positive reaction. In a negative test, no turbid precipitate forms. Observations are made with the naked eye alone.

The test depends upon the precipitation of an excess of the euglobulin fraction which is not water soluble. Whether it is due to an

increase in the normal euglobulin fraction or to some special euglobulin formed in Kala-azar serum is not clear. On theoretical grounds, one would expect this to be a good test for hyperproteinemia, since the protein fraction increased in this condition is usually euglobulin. Unfortunately, studies of the globulin precipitation test by the Sia technique are not available for other types of hyperproteinemia. Therefore, opinion as to the worth of this procedure should be reserved until more data is available.

Williams and Gutman²⁰ report that the Ray globulin test (a somewhat similar reaction) was negative for the hyperproteinemia due to lymphogranuloma inguinale. This is somewhat suggestive that the euglobulin increase in different diseases may be due to the formation of a special protein fraction.

SUMMARY AND CONCLUSIONS

Hyperproteinemia comprised 2.4 per cent of routine blood protein determinations made during 1936 in the clinical laboratory of one general hospital. It is found consistently enough in dehydration, multiple myeloma, lymphogranuloma inguinale, sarcoid of Boeck, leprosy, Kala-azar and schistosomiasis to be of diagnostic significance. It may rarely occur in a few other diseases. In practically each instance, the increase is mainly in the globulin (more specifically the euglobulin) fraction, with an absolute diminution of albumin and a marked reversal of the albumin-globulin ratio. Even normal total protein values may be significant if the globulin shows similar increases. A few cases are on record in which Bence-Jones protein or fibrinogen constituted the protein increase. The pathologic physiology of hyperproteinemia may also be of diagnostic significance. An abnormal protein increase of the blood may cause rouleau formation of the erythrocytes, increased blood sedimentation rate, spontaneous precipitation of blood proteins, precipitation of blood proteins by Hayem's solution, discrepancy in acid-base equivalence, failure of the clot to retract, rapid coagulation of blood, intravascular autohemagglutination, and anticomplementary Wassermann reactions. Hyperproteinemia probably has little or no effect on the blood calcium level, renal function or oncotic pressure of the blood. The Takata-Ara reaction, the formol-gel reaction and globulin precipitation test

are usually positive in the presence of hyperglobulinemia and may be valuable simple procedures for detecting hyperproteinemia

END NOTE

Since this paper was prepared, two important studies dealing with this subject have appeared. Gutman and Wise⁹³ found the formol-gel reaction to be positive in every one of thirteen cases of hyperproteinemia associated with lymphogranuloma inguinale and multiple myeloma. The positive results were correlated with the hypereuglobulinemia present in these diseases. In one case the test was positive even though the globulin increase consisted only of the pseudoglobulin I fraction. The test was also positive in liver cirrhoses with hyperglobulinemia but with normal total proteins. These results, combined with those by Bing, demonstrate convincingly the value of the formol-gel reaction in detecting hyperproteinemia.

Gomori and Podhradszky⁹⁴ produced dehydration in animals by pyloric obstruction. The hyperproteinemia which resulted was found to be associated with a reversal of the albumin-globulin ratio. This confirms the findings noted by Talbott.⁶ In addition, these workers found the colloid osmotic pressure of the hyperproteinemia in dehydration to be increased sufficiently to counteract the glomerular filtration pressure and cause renal failure. These findings are contrary to previously reported values of the colloid osmotic pressure for the hyperproteinemia associated with multiple myeloma. The effect of hyperproteinemia on renal function is still an open question and needs further elucidation.

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SOME INDICATIONS AND CONTRAINDICATIONS IN THE MEDICAL TREATMENT OF NEPHROLITHIASIS*

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THE following facts have all been well established (a) hyperparathyroidism is a metabolic disease entity, (b) in hyperparathyroidism there is a disturbance of calcium and phosphorus metabolism and among other things an increased calcinuria and phosphaturia, (c) patients with hyperparathyroidism have a marked predisposition to develop kidney stones, consisting largely of calcium phosphate. There is certainly strong circumstantial evidence that the cause of the calcium phosphate stones is the increased calcium and phosphorus in the urine. The above evidence has led to a renewed interest in possible metabolic factors which might influence the formation of the kidney stones which are not due to parathyroid disease. It, furthermore, has focused attention on the composition of the urine in relation to the formation of stones. It is the object of this paper to discuss these aspects of the problem as they concern the case of a young man who died of bilateral kidney stones.

The patient, single, aged twenty-seven, came to the Massachusetts General Hospital in December, 1936, with the diagnosis of bilateral renal calculi. The following points in his history are probably of importance.

(a) At the age of twenty he suffered from tiredness, albuminuria was found, he was treated with alkalis (sodium bicarbonate and "Crazy Crystals") and a low protein high milk diet.

(b) At the age of twenty-three the patient had his first attack of renal colic on the left side, a roentgenogram revealed a pea-sized stone in the left kidney, this was removed.

(c) Six weeks after this operation the patient had an attack of right-sided renal colic, roentgenograms showed multiple stones in both kidneys, during the next two years there were multiple at-

* From the Medical Clinic of the Massachusetts General Hospital

tacks of colic, 211 cystoscopies, and multiple operations (3 left, 1 right)

(d) Ten months before entry five small stones were removed from the right kidney pelvis, and a nephrostomy tube was left in

(e) During the months immediately prior to entrance a sustained attempt with ammonium chloride and hydrochloric acid, etc., to acidify the urine was made but the urine remained alkaline, mandelic acid was tried to sterilize the urine, the stones continued to form even more rapidly

Physical examination was non-contributory except for evidence of loss of weight (60 lbs during illness), the operation scars, and a right nephrostomy tube

The roentgenogram of his kidneys (fig. 1) showed bilateral kidney stones and hydronephrosis

The urine examination showed a moderate amount of albuminuria, a fairly good range of specific gravity (1.015 to 1.020), a pH of 7.0 to 7.5 and many white cells and a few red cells in the sediment. There was no retention of nonprotein nitrogen, but a marked reduction in phenolsulphonephthalein excretion

Such in brief were the essential facts on admission. One of the first questions in this clinic with such patients is whether hyperparathyroidism is or is not present. The fact that there were no bone symptoms and no roentgenographic evidence of bone disease does not mean that hyperparathyroidism may not have been present. Thus in a series of thirty-five cases of proved hyperparathyroidism from this clinic twelve cases had no bone disease¹. The patient's serum calcium level was found to be 10.6 mg per 100 cc, his serum inorganic phosphorus level, 4.6 mg per 100 cc. These values, being within normal limits, were against the diagnosis of hyperparathyroidism where one expects a hypercalcemia and a hypophosphatemia. However, before absolutely dismissing the diagnosis, one should consider certain possible exceptions to the usual chemical pattern pertaining in hyperparathyroidism

In the first place, with renal insufficiency and a rising nitrogen retention one expects an elevated inorganic serum phosphate level. In cases of hyperparathyroidism with marked renal insufficiency, the hypophosphatemia may no longer be present². In such patients the nonprotein nitrogen of the serum should also be high. In the

patient in question it was only 23 mg per 100 cc. Therefore, the lack of hypophosphatemia was not to be attributed to renal insufficiency.

Secondly, the serum calcium value should be analysed in relation to the serum protein value. The serum calcium is mostly in two forms, calcium ions and calcium-bound-to-protein. The amount bound-to-protein (normally about 50 per cent) depends largely on the amount of protein. In hyperparathyroidism it is primarily the calcium ion fraction which is elevated. It is possible, therefore, that in a patient with a mild degree of hyperparathyroidism a small elevation of the calcium ion fraction may be offset by a decrease in the calcium-bound-to-protein fraction as the result of a low serum protein so that the total serum calcium value may remain normal. Such a case was reported by Albright, Sulkowitch, and Bloomberg.¹ The serum protein of the patient here discussed was 5.9 Gm per cent. This value was not sufficiently low to materially affect the serum calcium value. Hyperparathyroidism, therefore, could be dismissed as a possible cause of the rapid stone formation.

It was, therefore, necessary to seek further as to the etiology of the stones. Stones which are so large, which form so rapidly, and which show up so well by roentgenogram are almost sure to be composed largely of calcium phosphate. One of the stones which he had passed was analysed and found to be composed largely of phosphates. There was no uric acid. Phosphate salts precipitate out only in an alkaline medium. Attention was, therefore, next focused on the acidity of the patient's urine. The urine was found at all times and under all circumstances to be alkaline (range of pH 7.0 to 7.5).

In the absence of extreme renal insufficiency where the kidneys cannot produce an acid urine, a constantly alkaline urine usually means a urinary infection with an organism which splits urea into ammonia. The urine culture on this patient showed *bacillus coli* and *bacillus proteus*. The latter is a urea splitting organism. The immediate cause of the formation of stones, therefore, was presumably a persistently alkaline urine, caused by *bacillus proteus* splitting urea.

In the presence of such an infection, usually enough ammonia is formed to outdo any measures which may be taken to render the urine acid. It should be pointed out that the usual best way of

FIG. 1



Roentgenogram showing bilateral kidney stones



producing an acid urine—namely, giving ammonium chloride—is particularly ineffective under these circumstances. The ammonia which in the blood has been changed to urea is excreted as such by the kidneys. Hence this therapy increases the urea in the urine and thus the source of the ammonia formation. With a proteus infection a vicious cycle is set up. The infection causes an alkaline urine, this causes the precipitation of phosphate stones, these lead to more infection and stones, etc.

Before the possibilities as to treatment of this situation are discussed, it seems of interest to speculate on the possible factors which contributed to getting the patient into this predicament.

The first link in a chain of unfortunate events occurred probably when, because of albuminuria, he was given alkalis (sodium bicarbonate and "Crazy Crystals") and a low protein high milk diet. This albuminuria may very well have been orthostatic, in any case the rationale of the therapy is not apparent. Reducing the protein in his diet meant that one was reducing the chief acid-ash component of the diet and thus favoring an alkaline urine. The giving of alkalis in addition probably insured the presence of an alkaline urine, in which the phosphates would all be out of solution. Finally the high milk diet with its high phosphate content must have resulted in there being a large amount of phosphate in the urine as most of the ingested phosphates are excreted in the urine. Thus the stage was set for the formation of a calcium phosphate stone and one did form.

Now it is obvious that everybody who takes alkalis and a high phosphate and calcium diet does not form kidney stones, likewise many cases with hyperparathyroidism do not form stones. Still it seems probable that any situation which leads to the precipitation of some salt in the urine as it is passed favors the formation of stones. The current wave of advertising about the dangers of acidosis and the foisting of all kinds of alkaline salts on to the public probably has a definite bearing on the formation of phosphate stones. The belief that lots of "good fresh milk" is very healthy may or may not be so, but in the occasional person it is going to favor stone formation. It is of interest that herbivorous animals have an alkaline urine, but have arranged to excrete their phosphates in their feces, carnivorous animals have an acid urine and excrete most of their

phosphates in their urine, man resembles the carnivorous animals as to the excretion of phosphates, but occasionally varies his diet or takes sufficient patent medicines so that he has the unfortunate combination of an alkaline urine high in phosphate

Another possible factor in the formation of the first stone may have been the decrease in the urea in the urine resulting from the low protein diet. There are certain compounds, called hydrotropic substances, which markedly increase the propensity of other substances to stay in solutions. Urea is such a hydrotropic substance.

What was the next link in the unfortunate chain of events? It took three years to form the first stone, this was removed, in six weeks there were multiple stones on both sides. It is obvious that from the time of the first operation the stone formation was markedly accelerated. It seems not unlikely that at that time the *proteus* infection became established and the alkalinity of the urine was increased.

One not infrequently sees transient *bacillus proteus* infections after urological procedures. Many cases quickly clear up, in others the infection becomes thoroughly established and chronic. In the author's limited experience no case of *proteus* infection has been encountered in a patient who has not undergone some urological manipulation. This is in marked contrast to the experience with *bacillus coli* infection.

The next link in the chain of unfortunate events probably occurred in the months just prior to admission. It was realized that it was important to get the urine acid. Ammonium chloride and hydrochloric acid were administered. The futility of such procedures in most cases of *proteus* infection has already been mentioned. But such therapy is not only futile, but it is actually very harmful. When ammonium chloride is administered, the ammonia is changed to urea and is in this form in the blood while the chloride remains as so much hydrochloric acid. This leads to an acidosis as regards the body fluids, this in turn leads to an increased mobilization of calcium and phosphate from the bones and an increase of these substances in the urine (compare treatment for lead poisoning). In the urine, as discussed above, the urea is turned back into ammonia by the *bacillus proteus*. The net result is that an increased amount of calcium and phosphate is being excreted into an alkaline

urine It is therefore not surprising that the stones grow more rapidly

With the realization on the part of the profession of the importance in many cases of obtaining an acid urine in the prevention of stone formation, there have occurred certain untoward results because the contraindications were not realized. In the first place the acid urine is important only for the phosphate stones, it will not benefit the oxalate stones, it is bad for the cystine and uric acid stones. Secondly, badly damaged kidneys cannot excrete an acid urine under any circumstances and pushing acid therapy may result in a severe body acidosis. The third contraindication is the one just mentioned. The acid therapy does one good thing—makes the urine acid—and one bad thing—increases the urinary excretion of calcium and phosphorus. If one succeeds in doing the good thing, the bad thing is no longer bad as the calcium and phosphate will remain in solution. If one does not succeed in doing the good thing, the bad thing is very bad. Therefore it is urged that in trying an acidification regime the urine be tested to see whether the desired result is obtained. If it is not, stop.

So much for the diagnosis and the events which may have contributed to the patient's condition on admission, what was to be done about it? The important thing was to eradicate the *proteus* infection. But how? There was no use trying such antiseptics as mandelic acid as they work only after the urine has been made acid by other agents. There are certain interesting possibilities in the therapy of *proteus* infection which are being tried but they are still in the experimental stage. For the time being one can only call attention to the problem and some of its difficulties but no solution can be offered.

But what about the patient? The chain of unfortunate events persisted. He died shortly after admission. At autopsy there was bilateral pyelonephritis with venous thrombosis and multiple septic infarcts in the lungs. It would seem that his case history presents an interesting lesson in what not to do, even if it fails to tell us what to do.

SUMMARY

The case history of a young man who died of bilateral kidney stones is reviewed and the following points are stressed:

I Lack of skeletal involvement does not rule out hyperparathyroidism as a cause of kidney stones

II Whereas in hyperparathyroidism one expects a low serum phosphorus level and a high serum calcium level, the former may not be decreased in the presence of renal insufficiency and nitrogen retention and the latter may not be elevated in the presence of a low serum protein level

III In the presence of a urinary infection with a urea splitting organism, the ordinary methods of acidifying the urine are usually futile, ammonium chloride administration is particularly futile as it increases the urea excretion in the urine and hence the source of the ammonia formation

IV Any regime which causes a constantly alkaline urine, especially if in addition large amounts of phosphates are ingested, may predispose to the formation of phosphate stones

V Whereas a regime which has as its purpose the acidification of the urine is indicated in most cases with a tendency to form phosphate stones, it is contraindicated

- (a) in the presence of uric acid, and cystin stones,
- (b) where there is marked renal insufficiency, and
- (c) where for any reason the desired acidification is not obtained (e.g. presence of a urea splitting organism)

VI Infections with the urea splitting bacterium, *bacillus proteus*, usually and maybe always follow instrumentation or operations on the genito-urinary tract, if the infection becomes well established in the kidney pelvis it is very difficult to eradicate, just what therapy should be tried is not clear

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Diseases of Joints

CHRONIC ARTHRITIS*

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"ARTHRITIS is a problem which is more or less hopeless" This is the consensus of opinion of practitioners of medicine. The great difficulty is always that of treatment however, although treatment is important, diagnosis is still more important. In order to diagnose correctly we must understand the pathology of arthritis and agree upon a uniform classification of its different forms. To begin with we will take up the question of classification.

The American Rheumatism Commission has been of considerable assistance in this matter. It has suggested the use of the terms atrophic arthritis (rheumatoid arthritis of the English) and hypertrophic arthritis (osteoarthritis of the English). However so many different terms have been used in the past that in order to make matters clear I offer the following table which shows at a glance the variously named conditions which now are included under the atrophic and the hypertrophic forms of arthritis.

ATROPHIC ARTHRITIS

- 1 Rheumatoid Arthritis
- 2 Proliferative Arthritis
- 3 Ankylosing Arthritis
- 4 Still's Disease
- 5 Metastatic Arthritis
- 6 Infectious Arthritis
- 7 Arthritis Deformans
- 8 Marie Strumpell Syndrome
- 9 Spondylitis Deformans

HYPERTROPHIC ARTHRITIS

- 1 Osteoarthritis
- 2 Degenerative Arthritis
- 3 Non ankylosing Arthritis
- 4 Menopausal Arthritis
- 5 Metabolic Arthritis
- 6 Von Bechterew's Syndrome
- 7 Senescent Arthritis

ATROPHIC ARTHRITIS—ETIOLOGY

The etiology of atrophic arthritis is a confusing problem. The

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work of Cecil,¹ Wetherby and Clawson,² and Burbank³ suggests that atrophic arthritis is a streptococcus infection. However, it is difficult to understand how it is possible for a streptococcus floating in the blood stream to do so much damage to the joints while the viscera and other systems remain relatively unharmed. The work of Pemberton⁴ on the other hand tends to place the responsibility on faulty carbohydrate metabolism plus the presence of focal infection. Focal infection is certainly a factor, but the matter of faulty carbohydrate metabolism I have been unable to reconcile with the fact that the patient with this disease is usually emaciated and is apparently badly in need of carbohydrates. He has no difficulty in utilizing them provided his digestion has not been upset by too much medication.

According to Small⁵ the patient with atrophic arthritis is extremely sensitive to the protein of streptococci. If this be true, then allergy plays an important part in developing the symptoms of the disease.

It is extremely difficult to believe that each of the above authors has a specific organism, yet all believe that a streptococcus is responsible for the disease. How a closed focus, harboring streptococci of low virulence, is capable of doing so much damage to the joints and yet so little to the viscera, regardless of whether it is due to bacteremia or toxemia, is hard to explain on any basis other than perhaps that of allergy. On the basis of allergy is it not possible that there may be some factor common to all streptococci that is capable of producing arthritis? It may be a protein or a toxin, although toxins are species specific. It is my belief that the real cause of arthritis can be found only if we work on the allergic theory. The prevalent view is that an antigen injected into an animal will produce antibodies specific to this antigen. The second injection of antigen will unite with its antibodies already formed, and this union acts either on, or in the cell, and so injures it that it liberates histamine or a histamine-like substance, which in turn acts upon the neurovisceral mechanism to produce anaphylaxis.

Let us assume then, that absorption from a focus of infection acts as an initial injection of antigen. It follows, since this focus persists, that a second and many future injections of antigen come from this source. It is my belief that the lowering of bodily resistance due to exertion or an intercurrent infection, such as a cold, or a fall of atmospheric pressure, as occurs during changes in the weather, may

bring about a release of antigen, and the union of this antigen with *reformed* antibodies may cause an exacerbation of the symptoms of the disease

PATHOLOGY OF ATROPHIC ARTHRITIS

Atrophic arthritis begins with a proliferation of the synovial membrane and the formation of granulation tissue over its surface. This gradually spreads and invades the cartilage, destroying it. As the process advances, the granulation tissue spreads over the articulating surfaces and beneath them. Approximation of the opposing granulating surfaces causes their adherence and the resultant fibrous tissue formation produces fibrous ankylosis.

There is an increase of fluid about the joint and mononuclear cells invade the periosteum. The bone marrow gradually is replaced by edematous fibrous tissue containing many osteoblasts and new capillaries, and the entire architecture of the joint may be destroyed. The soft tissues are infiltrated and soon there is atrophy of muscles, tendons, ligaments, cartilage, bone, etc. Contractures, dislocations, fibrous and bony ankylosis, and complete obliteration of the joint cavity with canalization are the result.

SIGNS AND SYMPTOMS

The terms atrophic, rheumatoid, proliferative, are used synonymously and apply to any of the types of the disease as has been mentioned. Ankylosing arthritis and arthritis deformans apply principally to the far advanced stages of arthritis in which ankylosis, dislocations, and other types of deformities are present. Atrophic, rheumatoid or proliferative arthritis affects males and females alike. The disease comes on gradually. The patient is usually thin and debilitated, if not at the onset of the disease, he soon becomes so. There is an associated secondary anemia, and there may be a low grade fever. The condition usually begins in the fingers, with soft swelling about the middle joint and the characteristic spindle shaped deformity. The knees are next most often involved. Swelling may assume fairly large proportions. There is fluid about the joint and crepitation on palpation. Soon the capsule becomes thickened and one feels a capsule surrounding the joint which apparently is much too large. There is a good deal of pain, accompanied by stiffness whether at rest or on motion. Change in the weather has a definite influence.

upon the joints, there being generally much more pain on cloudy days or before a storm under which circumstances relief comes with the rain.

As the disease progresses, nearly all the joints may be involved. There are instances in which not one joint is spared. There is ulnar deviation of the hands, the feet become flat, the spine rigid and pain is intense. Soon, because of the destruction of tissue, relaxation of ligaments, and atrophy of bone, muscle and tendons, dislocations may be manifest, and as nature attempts to repair the damage there is fibrous and bony ankylosis. This now is what is known as *arthritis deformans* and *ankylosing arthritis*. The patient complains always of being cold, the skin is usually dry and atrophic, there is a good deal of loss in weight, and anemia is marked. The appetite is poor and often there is indigestion. The sedimentation rate¹⁶ is increased.

Still's disease¹⁵ was first described in 1897 as a polyarthritis occurring in childhood. The condition is not clearly defined as a separate entity. It has often been called "*arthritis deformans of childhood*." Some writers believe this to be a form of atrophic arthritis occurring early in life. Usually it begins in the spine when the onset is chronic, however, when the onset is acute it is not unlike the acute arthritis of adults. There is usually generalized lymphatic involvement with splenomegaly and sometimes with hepatic enlargement. The later stages of the disease do not differ from the far advanced atrophic arthritis of adults.

In the Marie Strumpell syndrome the spine primarily is involved. It begins with pain in the back, chest expansion becomes restricted, and ankylosis ensues as the result of ossification of the anterior common vertebral ligament. At a late stage the typical symptoms of atrophic arthritis occur in fingers and other joints.

Spondylitis deformans is atrophic arthritis involving the spine alone. It is usually gradual in its onset, beginning with pain in the back. The final result is a convex spine. There is considerable ankylosis present. This type of spondylitis is very painful, but not so incapacitating as other forms since frequently no other joints are involved.

Metastatic or infectious arthritis may begin as an acute or a chronic disease. When acute, it is usually ushered in by a chill and sudden rise of temperature, accompanied by prostration. The joints

become painful, hot, swollen, and red. The usual diagnosis is that of acute rheumatic fever. It is uncommon under the age of thirty and usually attacks persons exposed to the weather. The fever may rise to 104° or 105° . The patient may be delirious, the tongue coated, the breath foul, perspiration is excessive, and breathing is rapid. On examination of the heart, one frequently finds murmurs at all the valves. The joint manifestations are unlike those of rheumatic fever in so far as they are not evanescent and the smaller as well as the larger joints are involved. The course is a stormy one, lasting sometimes from six to eight weeks through the acute and subacute stages. As the acute inflammation subsides, there is residual stiffness and pain. Focal foci of infection are as a rule evident. The disease frequently goes on into a chronic stage, but even then, with proper treatment, the patient often makes a good recovery. I have seen instances in which there has remained a loud blowing systolic murmur at the apex, which in time has completely disappeared.

TREATMENT OF ATROPHIC ARTHRITIS

Assuming that the focus of infection is acting as the sensitizing agent, it is reasonable to assume that if we can find some substance, which, when injected into the patient, will produce specific antibody response, we have fulfilled the requirements as described in the paragraph on etiology. In the so-called streptococcus cardioarthritides soluble antigen, described in a previous paper,⁶ this substance may be presumed to be present. It is also present in filtrates made from other streptococci.

Warren Crowe,⁷ the pioneer in vaccine therapy, has been using vaccines in doses of one thousand or less organisms and producing reactions such as are to be described. The doses of streptococcus cardioarthritides soluble antigen are more or less on a par with those advocated by Crowe, except that the organisms have been filtered out and only the filtrate used. It is the writer's belief that better results are obtained by the use of filtrates than by vaccines.

Before going into the question of dealing with focal infection, I wish to consider a few points in the treatment of this disease which are of great importance. As was stated above, atrophic arthritis occurs in the asthenic individual whereas the hypertrophic variety occurs in the sthenic. Although the general principles of treatment,

which will be stated below, apply equally to both types of arthritis, yet there are certain details of treatment peculiar to each type. The resistance of the patient suffering from atrophic arthritis should be built up. As far as food is concerned, anything that will agree with him should be permitted freely. In this respect atrophic arthritis should be treated as we treat tuberculosis. Anemia should be combated by the use of iron, arsenic and an appropriate diet. Ankylosed joints and deformities should be overcome by using the methods of the orthopedic surgeon.

Physiotherapy is valuable, particularly the use of heat and sunlight. Massage should be confined to the muscles and used only so long as pain is present, there should be no manipulation of the joints until pain has subsided.

Rest is an important factor in both types of arthritis. A certain amount of exercise is necessary in the atrophic form, but it must be taken with considerable care. The patient should not be subjected to any kind of vigorous exercise until free from pain.

Foci of infection should be eradicated. Strange as it may seem, more is taught on the subject of focal infection in arthritis than perhaps in any other disease, yet less appears to be done about it. We often see patients who have been suffering for many years with this disease and yet infected teeth and tonsils are allowed to go unheeded. When such obvious foci of infection are neglected, what are we to expect when there is hidden infection in the prostate, cervix, gall-bladder, colon, and elsewhere? Whenever the tonsils are diseased, they should be removed. Indeed it is my opinion that whenever tonsils are present they should be removed. Laryngologists say that the only way definitely to decide whether or not a tonsil is diseased is to examine sections of it under the microscope.

There are no organs in the human body that have been so mis-treated as the teeth. We often see young people, with or without arthritis, wearing complete artificial dentures following the removal of all the teeth. The dental profession is making great strides in educating the public that roentgenograms are necessary before extraction is done. No one questions that a tooth with a diseased apex should be removed. Attempts to treat such teeth conservatively have not proved successful. Often individuals who are toothless are found to harbor diseased roots in the gums or bone, and these, of

course, may act as foci of infection. Devitalized teeth should be removed regardless of roentgen ray findings.

The gallbladder, cervix, prostate, and sinuses are very common sites of infection. Needless to say they are often overlooked. Extreme care should be exercised in eliminating them as possible foci of infection.

For constipation high colonic irrigations are of value together with laxative drugs. The strong fluid extract of cascara sagrada, given in graduated doses to meet the patients' requirements, is as good a remedy for this purpose as any we have. The patient should be instructed to find out what quantity is necessary, and this quantity should be taken daily for a week. Gradual reduction in the amount may be made over a period of months. I have seen patients completely relieved of their constipation by this method.

One should not stop at the removal of foci of infection. It is my belief that if foci are removed within six months of the onset of the arthritis, usually the patient recovers without further treatment. However, if the foci are not promptly located and removed, the patient becomes sensitized to the products of the infection and then merely the removal of the focus of infection does not desensitize the patient. The organisms normally present in the nasal passages and the gastro-intestinal tract now take up the work of maintaining sensitivity. The procedure is to desensitize the patient and this may conveniently be done by the use of streptococcus cardioarthritides soluble antigen. The technique as to the manufacture of this product is described in another paper.⁸

ANTIGEN TREATMENT

One twentieth cc of streptococcus cardioarthritides soluble antigen, dilution 10 to 15, is administered subcutaneously as the initial dose. The patient is instructed to keep an accurate record of any change that may occur in his condition from day to day until seen again by the physician. Symptoms after the injections come anywhere from a few hours to a few days. They are in the nature of a so-called reaction manifested by nervous irritability, restlessness followed by wakefulness, pain in the affected joints, sweating, paresthesias, numbness, disturbance of taste and smell, sore throat, acute exacerbation of sinusitis, diarrhea, occasionally nausea, rarely vomiting, often a feel-

ing which the patient describes as something he "cannot explain." The reactions usually last from a few hours to a few days. They may be focal, such as pain in the joints, general, such as nervousness, or localized, such as sore throat, acute sinusitis, diarrhea, nausea or vomiting. When localized symptoms occur, they are of extreme importance in identifying the offending focus.

The general constitutional symptoms appear to be due to activity of the sympathetic nervous system. Sweating, fatigability, coldness of the skin, alteration of skin temperature, blanching and redness of the skin, leave little doubt in the minds of most workers that the sympathetic system is involved in arthritis. The work of Rowntree and Adson⁶ helps considerably to substantiate this. One of the most important symptoms of the disease, next to the joints themselves, is despondency. There are instances in which this is so pronounced that suicide is seriously considered by the patient. Despondency is certainly a part of the disease arthritis and psychotherapy is therefore essential. Following the depressed reaction, which may be termed a primary one, there is usually a period of euphoria which may last a few days, and then a secondary reaction in the nature of more pain in the joints, often more than the patient has ever had before.

Reactions should come on within twenty-four hours after injections. This is what we should strive for. If the reaction is primary, such as despondency for example, then an attempt should be made to bring the secondary reaction closer to the primary. It will be noted that as this is brought about by the reduction of the dose of antigen, the primary reaction symptoms will gradually disappear. The secondary reaction now takes the place of the primary. It should now be the purpose to reduce this reaction to a minimum. This is done by further reducing the dose of antigen.

In this way a point will be reached at which there is practically no reaction manifested and there is gradual improvement. At this point the dose should be maintained. Many patients go on to complete recovery in this way. On the other hand, it often happens that the patient will improve for a time, and then suddenly there is again manifested marked focal and constitutional symptoms. At this time one of two things must be done. Should the reaction be severe and come on within a few hours following the injection, it usually means

that a substantial increase in dosage is necessary, and when the dose is increased almost immediate relief is obtained

Antigen should be administered subcutaneously and at no less interval than every four days, but we should strive to prolong the feeling of freedom from pain for a greater interval. This is accomplished by a minute increase in the dose. As the dose is increased, the interval between treatments should be correspondingly lengthened. However, should the reaction come on about twenty-four hours after the injection, this means that the patient has become reactivated and a reduction in the dosage becomes necessary as before.

There may be instances in which there is no reaction at all. In such cases a gradual increase in the quantity of antigen is indicated. It will be found that the patient will improve without reaction and so long as a quantity is reached that is evidently responsible for this improvement, that quantity should be maintained until no more improvement is noted, the dose should then be increased.

In a previous article⁶ a summary was presented of forty-seven cases treated at the Arthritis Clinic of the Jefferson Hospital. Without presenting case histories, I wish to state that many hundreds of patients have since been treated with results which substantiate the statements made in previous papers.

FEVER THERAPY

Hyperthermia or fever therapy as administered with the Kettering hypertherm, hot packs and diathermy has been used for the treatment of arthritis. It has been of no benefit except in gonorrhreal arthritis. At the present time one cannot be in the least optimistic about its use in atrophic arthritis.

VACCINE THERAPY

As has been stated, Cecil,¹ Wetherby and Clawson² and more recently others have treated atrophic arthritis with vaccines by the intravenous route. Good results are reported. We have thus far been unable to repeat these results. It is possible that our technique is in some way erroneous. We have also been unsuccessful in isolating streptococci from the blood stream.

On the other hand we have been more successful with treatment

as described by Crowe⁷ and Burbank⁸ We believe this to be due to the minute doses of vaccine used

The use of typhoid vaccine has a place in the treatment of atrophic arthritis, since the reactions produced may perhaps stimulate the formation of antibodies These reactions are much more severe than those observed after ordinary vaccine therapy The vaccine is useless unless given intravenously

JAUNDICE

Hench¹⁷ made observations on the effect of intercurrent jaundice induced by cinchophen and other drugs in atrophic arthritis Fourteen of sixteen patients obtained partial or complete relief from symptoms coincident with the onset of jaundice

Wyatt and Thompson¹⁸ have recently reported jaundice experimentally produced with encouraging results, but this work is still in its experimental state However, it is a great step forward, and promises to give us a new lead as to the etiology of this disease

POSTURE

In atrophic arthritis as well as in hypertrophic arthritis faulty posture may be associated with deformity of the feet Posture is here not the cause but the effect of involvement of the feet, and correction frequently adds considerably to the comfort of the patient More about this will be stated under the treatment of hypertrophic arthritis

SHORT WAVE THERAPY

Short wave therapy is yet too new to recommend for treatment of arthritis Here we are treating effect rather than cause Patients are apparently improved early in the treatment, but symptoms soon reappear

VITAMIN THERAPY

It has been suggested that vitamins be used exclusively or as an adjunct in the treatment of atrophic arthritis Vitamins B, C, and D have been recommended Doses as high as a million units daily have been prescribed over a period of weeks and even months In the writer's experience, as a specific, the treatment has neither a theoretical nor a practical basis, however, as an adjunct, in the usual doses in which vitamin is prescribed, it is to be recommended in view of the fact that we are dealing with a debilitating disease

ANALGESICS

In the acute attack, salicylates, if tolerated, are of great benefit. They should be administered in ascending doses until the point of tolerance is reached. This may be as high as three drams daily. The dose should then be slightly decreased and maintained at that level until the patient is well out of the acute attack.

Salicylates are also of benefit in chronic atrophic arthritis, but are best used in the form of acetyl salicylic acid in the doses of 10 to 15 gr three times daily after meals.

Calcium orthoiodoxybenzoate¹⁰ is of some assistance. In a group of 125 cases, 24 per cent were unable to tolerate the drug. In the rest of the group 4 per cent. were cured of the disease, 32 8 per cent were very much improved, 16 8 per cent were improved, and 22 4 per cent were unimproved. It does not affect the red or white blood cells, it has no effect upon the kidneys or blood pressure. This drug should also be given in ascending doses, beginning with 7 5 gr three times daily, and increasing the dose by 7 5 gr until improvement occurs. The drug is then continued at this dose. The maximum dose should not exceed 30 gr three times daily. In the beginning of treatment, if gastro-intestinal symptoms develop, the drug should be discontinued, however, if the patient has been taking it for some time, and these symptoms then come on, a rest period of a few weeks is indicated.

Phenacetin, amidopyrine, acetanilid are helpful particularly when used in combination with codein and acetyl salicylic acid for the relief of pain.

Cinchophen or its derivatives have no advantage over the above named drugs.

HYPERTROPHIC ARTHRITIS—ETIOLOGY

As has been stated, hypertrophic arthritis occurs more commonly in women. Since it begins with the menopause,¹¹ it necessarily follows that if the disease is of metabolic origin, that the ovary and thyroid are factors to be considered. The work of Monroe¹² would indicate that hypothyroidism is a very common finding in this disease. Although this is true in my experience, still I have not found it quite so regularly. Nevertheless, it is a matter of importance and should certainly be investigated in each case.

A subject of greater importance is the question of the ovary. Symptoms of the menopause are so often present, that one frequently feels that hypertrophic arthritis is merely another manifestation of this period of life.

The work of Pemberton emphasizes the importance of the gastrointestinal tract. Faulty carbohydrate metabolism and vitamin B deficiency are matters to be reckoned with. Although blood sugar determinations are repeatedly normal, one does find that the sugar tolerance test indicates a lowering of carbohydrate metabolism. Women at this period of life are notoriously constipated, and they suffer chiefly from the flaccid type. The work of Fletcher¹⁸ indicates that the condition of the bowel is a factor. To determine the influence of vitamin B as an etiological agent is difficult, although evidence appears to point to its influence on the tonicity of the large bowel.

The majority of these patients are obese. This would indicate a metabolic disturbance. Although the basal metabolic rate is seldom below minus 15, nevertheless, most of these patients have a basal metabolic rate on the minus side.

Posture is by far the most important of all etiological factors in hypertrophic arthritis. Flat feet are almost always present. There is bulging of the ankles to the inner side, the longitudinal arches sag, while the knees present signs and symptoms of stress and strain at the internal condyles. This syndrome is easily discernible if the rule of the orthopedist is applied, namely, an imaginary line dropped from the tibial tubercle perpendicular to the floor should normally meet another line extending posteriorly from a point between the first and second toes. This of course applies when the patient is in the erect posture on her bare feet.

PATHOLOGY OF HYPERTROPHIC ARTHRITIS

The primary change is in the articular cartilage, consisting chiefly of an erosion with exposure of the ends of the bones. In an attempt to compensate for this loss, there is hyperplasia of cartilage with resultant irregularity of the joint surfaces. Soon the epiphysis is invaded, there is deposition of bony tissue, and as an end result hypertrophy occurs. In this way are formed the familiar Heberden's nodes. There is no proliferation or granulation tissue formation, no tendency

towards ankylosis, but the exposed bony surfaces become smooth, shiny and hard, while the remaining cartilage becomes ossified. About the margin of the joints is usually found numerous cartilaginous nodules, pedunculated and formed from the synovial membrane. These cause a "locking" of the joint and are commonly known as "joint mice."

SIGNS AND SYMPTOMS

The terms hypertrophic arthritis, osteoarthritis, degenerative arthritis and non-ankylosing arthritis may be used interchangeably, since they designate the same conditions and are applicable to all the types of the disease now to be described.

When we speak of menopausal arthritis, we imply that it is present in the female. It is the type which comes on at, near, or during the menopause, whether artificial or natural, and is usually accompanied by the symptoms characteristic of the menopause. It begins with the characteristic Heberden's nodes, that is, the symmetrical enlargements of the distal joints of the fingers. Stiffness, soreness, and sometimes pain is present in the knees. The patient is particularly prone to complain after resting or on going up or down stairs. Pain is not intense, but very annoying. It is rarely incapacitating. The distal joint of the finger may show a tendency to deformity by a deviation to the ulnar side of the hand. Rest usually relieves discomfort. The patient is usually obese and accompanying the symptoms of the menopause are usually found the signs of cardiovascular renal disease with hypertension. Flat feet and postural defects are almost always present. Laboratory studies, including the sedimentation rate, are usually negative.

Von Bechterew's syndrome is hypertrophic arthritis of the spine. It occurs in old age particularly in the individual who has had laborious occupations, which have caused him to become "stooped" or "round shouldered." The individual whose occupation has necessitated the carrying of heavy loads on his back is most likely to present this syndrome. This is the type of hypertrophic arthritis which sometimes shows ankylosis. However, the ankylosis is not due to a proliferative process, but to pressure contacts of the bodies of the vertebrae against each other. The pressure has been of such long

standing that the approximating bones have joined as one. There is no pain present, but stiffness is predominant.

Senescent arthritis is that type of hypertrophic arthritis occurring in old age. It involves the fingers and knees as has been described under menopausal arthritis, but is painless and non-inflammatory. There may even be an absence of stiffness. It occurs in both males and females alike, and is practically never incapacitating.

The statement that hypertrophic arthritis occurs in old age is a common belief. However, the work of Myers, Keefer, et al.¹⁴ tends to substantiate the idea that degenerative arthritis, at least, in the knees, often begins at a very early age. As a rule, it is symptomless and the patient is unaware of its presence. If such is the case, it would seem rather difficult to believe that there can be any relationship between the two types of arthritis. This is one more step forward in substantiating the present classification. It would definitely tend to relieve us of the idea that degenerative arthritis is infectious in its origin. It is likewise difficult to believe that this process is the result of normal wear and tear of the joint cartilage, since the identical process does occur sometimes quite rapidly in the fingers of individuals free from the "humdrum" of the kitchen.

TREATMENT OF HYPERTROPHIC ARTHRITIS

The treatment of hypertrophic arthritis is relatively simple. We must bear in mind, first of all, that the patient has passed through a period of life during which she has neglected her health. As a rule she has borne children and her time has been so taken up with rearing her offspring that she has completely forgotten that her own welfare is important. We usually find that the patient is not only suffering from the symptoms of the menopause, such as hot flashes and nervousness, but from obesity, hypertension, nephritis, myocarditis, and postural defects.

It therefore follows that the individual is not only suffering from aches and pains in the joints, but also from general medical difficulties, all of which must be carefully looked into and cared for.

It is not necessary to discuss here the medical treatment of the climacteric, of myocarditis, of hypertension, or of nephritis. However, obesity and posture are matters closely related to the disease hypertrophic arthritis and these will be discussed.

It is difficult to conceive how nature could provide us with skeletal systems which might hold equally well 120 pounds and 240 pounds. However, apparently this is what is expected for we so often see individuals who all their lives have weighed 120 to 150 pounds suddenly increase their weight to 175 or 200 pounds and over. This sudden ontake of weight would probably do little damage if the posture were normal. However, in the presence of flat feet and faulty posture, the stress is so great that soon the knees begin to grow stiff and painful. Therefore, it is needless to suggest that under these circumstances a weight reduction regime is in order. We suggest the following:

LOW CARBOHYDRATE DIET

Avoid

- Sweets of any kind
- Food which is made from flour
- Berries and bananas
- Beans, peas, potatoes, rice, and corn
- Cereals

The above diet is easily remembered. It is very unpleasant to follow during the first few weeks but the patient soon becomes accustomed to it and loss of weight is gradual enough to cause no harm to the patient. The use of drugs as weight reducing measures, in the face of a normal basal metabolic rate, is not only contraindicated but dangerous.

The matter of posture is almost as simple as that of weight. As has been stated by orthopedic rules, one can easily determine whether or not the posture is faulty. In the presence of flat feet, one must consider corrective shoes containing

- 1 Rigid shank
- 2 Longitudinal arch support (stationary)
- 3 Wedges in heels to compensate for bulge at the ankles
- 4 Metatarsal pads when the metatarsal arch is not functioning properly

The use of drugs is seldom necessary except when a mixed arthritis exists, i.e., a combination of the two types.

Foci of infection should always be dealt with as described under the treatment of Atrophic Arthritis.

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(FORTY-SEVENTH SERIES—1937)

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